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REGULAR DEPARTMENTS

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 79 JANUARY 1958 NUMBER 1

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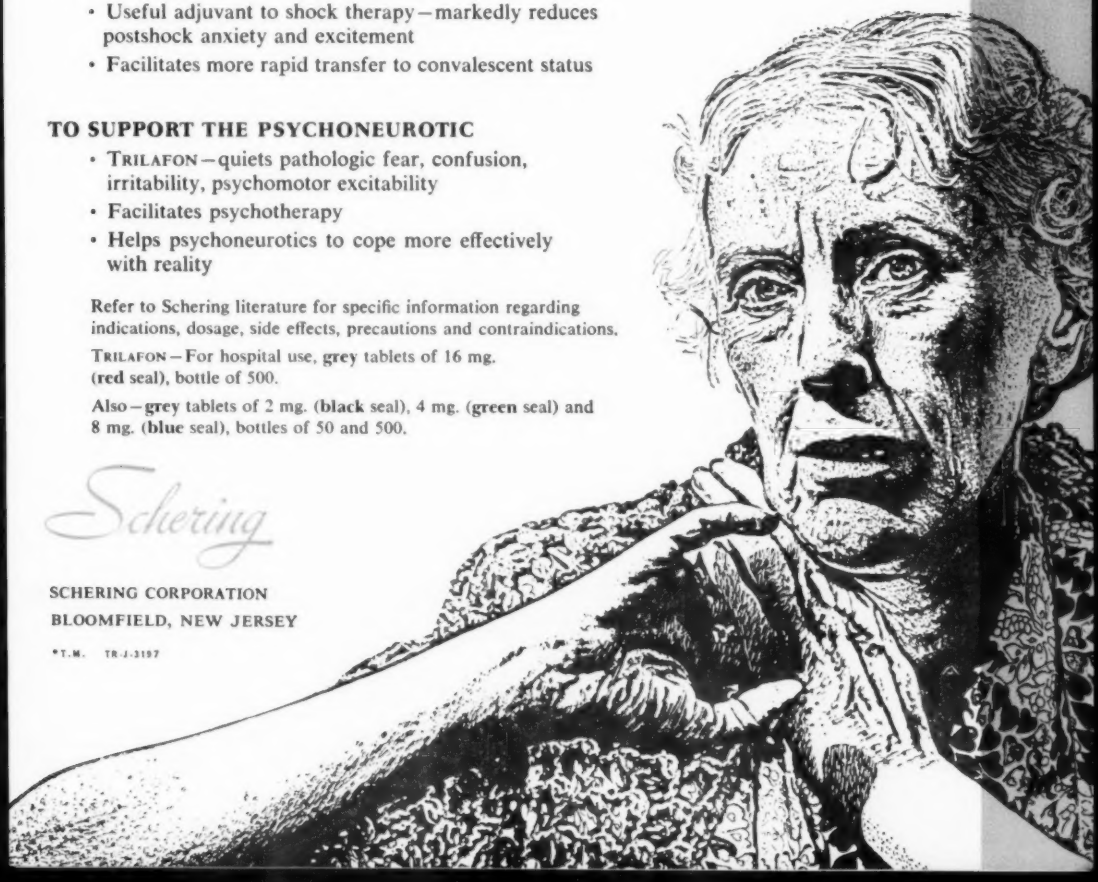

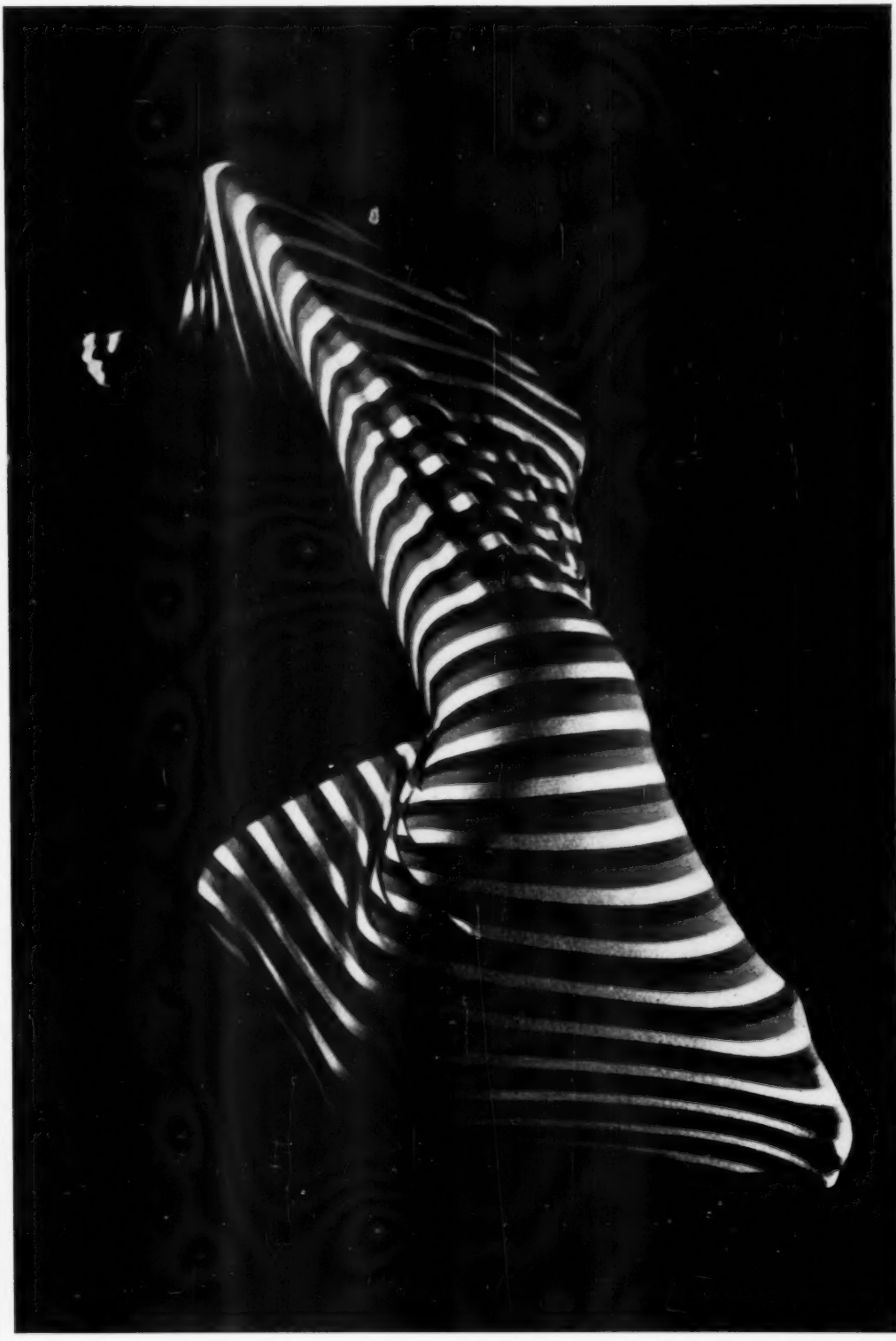

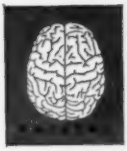

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SECTION ON
NEUROLOGY

Treatment of Pituitary Adenomas

Surgery Versus Radiation

GILBERT HORRAX, M.D.,† Boston

Pituitary adenomas, either chromophobe or chromophile, are a relatively frequent type of intracranial growth. In our total series of 1963 brain tumors seen at the Lahey Clinic through the year 1955, there were 335 adenomas, representing 17% of all tumors. Of this number, 141 were verified pathologically (1 by necropsy, the other 140 surgically), whereas in the case of the remaining 194 the diagnosis was made without any reasonable doubt by the finding of a greatly enlarged sella turcica by roentgenogram, together with optic nerve atrophy, visual field changes, or other characteristic pituitary stigmata, such as acromegaly.

In the early days of this century the only known treatment capable of reducing the size of pituitary adenoma, thus relieving pressure on the optic nerves with restoration of vision, was the operative removal of varying amounts of the growth. This was accomplished for many years by the so-called transsphenoidal procedure, with reasonably good results and an operative mortality of between 4% and 5%. The five-year mortality from recurrence after the transsphenoidal operation was rather high, however, varying from about 20% to 32%. For this reason, the intracranial operation has been utilized by most neurosurgeons since the late 1920's, and, although the immediate mortality with this method ranges from 12% to 14%, because of a more radical attack on the large intracranial extensions when these are present, the five-year mortality with this method is less than 10%.[1]

Although some attempts to treat pituitary adenomas with radiation were made as early as 1909,[2,3] it was not until the middle 1920's that any headway was made in this respect, and even then x-ray treatment was utilized very largely as an adjunct to surgery, after the adenoma had been removed to a greater or less degree. It was soon evident, however, that patients who had had radiation following their surgery remained freer of recurrence for longer periods than those who had not been given this treatment; so it was logical to assume that radiation should be given a trial before surgical removal was undertaken.[4] This, therefore, began to be done with greater frequency during the 1930's and 1940's on patients who were not suffering too greatly from visual loss; but, although at times some strikingly brilliant

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From the Department of Neurosurgery, the Lahey Clinic.

The Massachusetts Institute of Technology supplied the 2,000,000-volt radiation sources and took responsibility for the physical aspects of this work.

Read before the Section on Nervous and Mental Diseases at the 106th Annual Meeting of the American Medical Association, New York, June 4, 1957.

† Dr. Horrax died Sept. 28, 1957.

results were recorded, on the whole it did not appear that more than 25% to 35% of patients showed adequate improvement or maintained vision at a useful level. Furthermore, in not a few instances patients finally came to be operated upon after a prolonged trial of radiation when vision was so greatly reduced that they were not benefited by the surgical removal of their adenomas.

This situation was extremely discouraging to neurosurgeons, and it was doubtless because of the high percentage of patients who had to be operated upon in spite of previous irradiation that this form of therapy was rather discredited and came to be used in most neurosurgical clinics with considerable misgiving, and then only on patients having relatively slight visual impairment.

This general feeling as to the efficacy of radiation for this type of lesion was ours until 1950, when we began to treat pituitary adenomas with the 2,000,000-volt apparatus at Massachusetts Institute of Technology, using the rotational method and giving a much larger tumor dose than had been employed previously, namely, 4000 r. It was apparent that this higher dose could be given without depilation or skin reaction, owing to the multiple areas through which the rays were received, and very soon it became obvious that most of the patients were doing well, so that surgical removal of their tumors was not indicated.

It was for this reason that after several years of use of this type of irradiation we felt it was incumbent upon us to review what had been accomplished in the treatment of these lesions both before and after the year 1950, when we had first started giving the higher radiation dose. The results of this investigation were most encouraging and were published in 1955.[5] At the time of that report, which tabulated results through 1953, we found that before 1950, when a tumor dose usually not exceeding 2000 to 2500 r had been given, 58.5% of the patients who had been so treated had to be operated upon because vision continued to deteriorate or was not held at a useful level. On the other hand, of the patients treated since 1950, and receiving a tumor dose of 4000 r by the rotational method with the 2,000,000-volt apparatus, only 18.4% eventually needed operation up to the time of that report.[5] We were aware then, and are now, however, that for the latter group a follow-up period of only one to five years was available, and it may be that when another five years has passed a higher percentage of patients will come to be operated on. On the other hand, it is known from past experience that recurrence of a pituitary adenoma is unlikely after a five-year period following any form of therapy.

Treatment Data

The purpose of the present communication is not only to bring our radiation data up to date, but also to outline briefly the results of treatment for pituitary adenomas by operation only, by operation combined with irradiation, and by irradiation only. It should be emphasized that this investigation is confined to the chromophobe and chromophile adenomas. Other lesions in the pituitary region, such as craniopharyngiomas, meningiomas, and other miscellaneous growths, are not included.

Surgery Only.—There were 54 patients who were operated upon without previous or subsequent irradiation. Forty-two of this number survived operation. The mortality in this group was the highest because of the urgency of operation, vision was greatly reduced, and in many instances a large intracranial extension of the adenoma was found. Thirty-seven of the survivors have been followed up from 1 to 20 years, with an average survival of 7.8 years and an average improvement period of 6.1 years. It is known that 28 of the 37 have lived from 5 to 20 years, and 23 have maintained their improvement for the periods they have lived.

Surgery After Radiation.—In this group there were 61 patients, 5 of whom died after their primary operations. Of the 56

survivors, all lived from a few months to 20 years, for an average of 7.1 years, and maintained improvement for an average of 6.5 years. Forty-six of the fifty-six were known to have lived from 5 to 20 years, 44 maintaining improvement for the periods they lived.

Radiation After Surgery.—Twenty-five patients were given a course of irradiation following the surgical removal of their adenomas. All but one of these have been followed from 1 to 16 years, and they have lived an average of 8.2 years, with improvement for an average of 7.2 years. Twenty-two patients are known to have lived from 5 to 16 years, and 18 maintained their improvement for 5 to 16 years.

It is perhaps of some significance that this group showed the longest average survival and maintenance of improvement, a fact stressed by others, notably Henderson, in reporting Cushing's series in 1939.[4]

For the sake of over-all statistics in the group of patients operated on, with or without previous or subsequent irradiation, it may be said that 17 of the 140 patients operated on died after their primary operations, a mortality of 12.1%. As stated elsewhere, and as found by others,[6] the mortality of patients with adenomas without large intracranial extensions who are operated on by craniotomy is between 2% and 3.9%.[1] In the large extensions, the mortality runs to over 30%; but it is only by heroic measures that some of these patients can be salvaged, and it is inconceivable that procedures short of a radical intracranial operation would accomplish anything for them. This is reflected by the fact that the five-year mortality from tumor recurrence for patients operated on by the transsphenoidal method ranged from 20% to 32%, whereas after use of the more radical intracranial procedure this rate has dropped to less than 10%.[1]

In our group of operative patients, 96 (78%) of the 123 survivors lived from 5 to 22 years, and of the latter, 89% maintained their improvement for the periods they lived.

Radiation Only.—We now come to the rather large group of patients, 194 in number, who have been treated by irradiation only. Their adenomas, therefore, have not been verified histologically, but, as noted previously, there can be little doubt as to their lesions, since roentgenograms showed that they all had an enlarged, ballooned-out sella turcica, as well as other pituitary stigmata, such as optic atrophy, visual field defects, acromegalic features, amenorrhea, or other characteristic evidences of pituitary disturbance. No doubt an occasional mistake in diagnosis will come to light in this group, but this will be so rare that statistics will not be changed significantly.

Of the total, there were 103 who had no visual disturbances but were treated because of glandular deficiencies, headaches, or to prevent the advancement of their acromegalic features. With these we are not concerned in this communication, because they would rarely, if ever, come into the operative category.

The remaining 91 patients had some degree of visual loss, varying from rather slight to severe impairment, and so far radiation alone has improved their eyesight to a useful level or held it at an adequate level if it was only moderately impaired, so that surgical removal of the adenoma has not been necessary.

It would seem highly significant that of these 91 patients with visual loss whose eyesight has been maintained at a useful level by radiation alone there were only 33 in the 17-year period, from 1932 to 1949, whereas the other 58 were treated in the 6-year period, from 1950 through 1955.

This comparison may be brought out in a more striking manner by the following figures: In the earlier period, 1932 to 1949, 89 patients were treated for visual loss primarily by irradiation only, but of this number 56, or 62.9%, were operated upon subsequently because vision was not held at a useful level. These figures differ slightly

from those in a previous publication, owing to a revision of the earlier series, but the percentage operated upon remains about the same.

In the more recent period, 1950 to 1955, inclusive, there were 66 patients with visual loss who received primary irradiation with the 2,000,000-volt apparatus by the rotational method. So far, only 8, or 12.1%, of these patients have had to be operated upon because radiation was ineffective. It must be reiterated, however, that the one- to six-year follow-up period may not be long enough to give the complete picture, but the difference in the two percentages is something that cannot be overlooked.

Comment

The most frequent question which has been raised as to the advisability of irradiation for pituitary tumors relates to any possible damage to that portion of the brain in the vicinity of the growth. In all the years we have been following the patients in the series represented here, no evidence has ever been disclosed to support such an assumption. The amount of radiation delivered to the tumor has always been kept well below that to which normal brain cells would be sensitive.

It is felt by some that radiation is likely to cause hemorrhage into an adenoma. A few instances of such an occurrence were present in the earlier years of our experience, but incidents of this kind have practically disappeared since we have been giving smaller doses over a greater length of time. In a very small number of patients a slight hemorrhage has at times been suspected, but by careful checking of the visual fields at weekly intervals, their vision has gradually cleared up without the necessity of operating. We feel that the tendency of hemorrhage to occur is definitely related to the larger daily doses which were given originally. This is a possibility to be kept in mind, however, and, obviously, if serious and rapid visual loss should occur during treatment or subsequently, prompt operative intervention is mandatory.

In regard to other questions concerning the effects of x-ray treatment, we have never felt that it caused any difficulties if an operation on the adenoma should become necessary, and we have not seen a cerebrospinal fluid leak as a direct result of irradiation, although one patient developed this complication one year after being treated with x-rays.

If radiation directed toward a pituitary adenoma has ever caused cataract, as has been suggested, it simply means that the rays have not been delivered through the correct areas of the skull.

Summary

The treatment of pituitary adenomas of both the chromophobe and the chromophile variety has undergone considerable change during the course of the past 50 years. In the early days, surgical evacuation of the adenoma was the only known method by which vision could be restored in these patients. Gradually it was found that a combination of operation followed by irradiation was more effective than operation alone, and this led to a trial of radiation before surgical therapy was undertaken. Until the advent of a higher x-ray dose (preferably 4000 r tumor dose), however, about 60% of patients receiving previous radiation had to be operated on because radiation alone was not effective. At the present time, after the larger tumor doses were given, preferably by the rotational method with the 2,000,000-volt apparatus, only 12% of our patients have had to undergo surgery in order to retain adequate vision.

The Lahey Clinic.

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ABSTRACT OF DISCUSSION

DR. BRONSON S. RAY, New York: Dr. Horrax' long experience and level judgment in neurosurgical affairs command attention and respect, and his reevaluation of x-ray treatment of pituitary adenomas is particularly timely and valuable.

Enthusiasm over the benefits of x-ray treatment has waxed and waned in the past 30 years. If one looks back over this period at the various reports, it is apparent that much attention has been given to the type of radiation and manner of its administration; the hope is always expressed that the shortcomings would be improved, if not abolished, by the perfection of better methods.

Dr. Horrax has drawn a comparison between the results of past treatment (before 1950), using the standard 200-kv. machine, and the better results since 1950, with use of the 2,000,000-volt machine, and there would seem to be no question of the improvement. The advantage of the higher-voltage therapy appears to be in the rapidity with which an arbitrary tumor dose of 4000 r can be delivered. But it is only fair to point out for those who do not have access as yet to the higher-voltage devices that nearly the same effect can be accomplished by the standard x-ray therapy machine, which is now usually of 250 kv. By using multiple (four) ports or a rotation device a tumor dose of 4000 r can be delivered in not more than 30 days with the 250-kv. machine, and without any identifiable difference in side-effects.

Of course, there are other devices for delivering destructive radiation to the pituitary, and, in the order of their energy ratio, the methods extant, though not available to all, are (1) the standard 250 kv. x-ray machine; (2) Co^{60} teletherapy, in which gamma rays comparable to those of radium are delivered; (3) the 2,000,000-volt x-ray via the van de Graaff accelerator (or with resonant transformer units); (4) Betatron, which produces x-rays from highly accelerated beta particles at 22,000,000-24,000,000 volts; (5) deliverance of deuteron or proton particles of 190 mev energy by means of a synchrocyclotron, as used by Tobias and Lawrence at the Donner Laboratory in Berkeley, Calif.

Doubtless other methods will appear in this rapidly developing field. So we can anticipate that we have not yet explored all the possibilities for treating pituitary adenomas with radiation. But it needs no extended discussion, particularly among neurosurgeons, to remind ourselves that there are other factors to be considered, not the least of which is the possibility of untoward effects of damage to adjacent neural structures that exists in all the present forms of irradiation.

The more immediate and practical questions may be noted: When may it be unsafe to initiate or continue radiation treatment in the presence of impaired vision, and how can one be sure that the incomplete return of vision when treatment is terminated might not initially, or even now, be restored by surgical removal of the adenoma? Dr. Horrax today and in previous writings, as well as many others, has pointed out the limits of our ability to diagnose with complete accuracy the exact nature of a lesion in or about the sella and the uselessness of radiation therapy in most of the commoner tumors of this region.

Most of all, it needs emphasizing that vision which is failing rapidly will probably be jeopardized by the initiation or continuation of therapy. It is imperative, therefore, that careful and intelligent evaluation of visual tests be made not only before treatment is started but daily, if necessary, during the period of treatment. Usually the person best equipped to do this from the standpoint of both experience and interest is the neurosurgeon, whereas too often the responsibility has been left to others, unable to evaluate the visual changes or intent only on employing a highly recommended treatment devised to avoid the hazards of surgery.

I feel that the hazards of modern-day surgery and its adjuncts for operation on the pituitary have in the past been overemphasized. My own policy has been to resort promptly to surgery in any case which shows significant defects in the fields of vision or reduction in acuity below reading vision in either eye. Though I am not prepared to give statistical results of this policy, I am satisfied that mortality is low (probably under 3%) and results are good. I have been influenced, I'm sure, by the number of patients who have presented themselves at our clinic, having been treated elsewhere by x-ray and having irreparable damage to vision.

Finally, I should like to refer to a recent and somewhat iconoclastic program instituted in our

clinic in the treatment of chromophile (eosinophilic) adenoma, which causes acromegaly. We have been impressed with the finding that some (perhaps many) acromegalics assumed to be benefited or controlled by x-ray therapy have in fact continued to have an actively secreting adenoma, causing subtle, unrecognized or disregarded changes which not only perpetuate their unhappy symptoms, but shorten their lives through the development of diabetes mellitus, hypertension, and cardiac failure. We have recently made a preliminary report on two acromegalic patients having total hypophysectomy who have shown a most gratifying and unexpected reversal of many of the unfortunate changes that occur in their disease.

In a word, I wish to commend and thank Dr. Horrax for this valuable contribution. Undoubtedly, radiation therapy in pituitary adenomas has something to offer, and no doubt can and will be improved upon, but it has not yet replaced surgery for the patient who needs it.

Etiology and Pathogenesis of Laminar Cortical Necrosis

Its Significance in Evaluation of Uniform Cortical Atrophies of Early Life

CYRIL B. COURVILLE, M.D., Los Angeles

One of the characteristic tissue responses found in the brain is that which affects selectively and to varying degrees one or more of the cellular laminations of the cerebral cortex. This lesion has been described under varying names, but is best known in the older literature as "status spongiosus," and more recently as "laminar (or pseudolaminar) necrosis." As the name implies, one or more strata of the cortex are altered more or less profoundly over appreciable extents of the covering gray ribbon, sufficiently to constitute a conspicuous architectural alteration.

It is my purpose to review briefly the history of this characteristic alteration, to note the development of concepts as to its etiology, to amplify its pertinent qualities in order to understand the total picture involved, to make clear its relation to the larger problem of cerebral anoxia, and to point out its importance as a significant feature of a group of diffuse, more or less uniform, cerebral cortical atrophies of early life which appear to account for a group of abnormal states, namely, cerebral palsy, mental deficiency, and epilepsy. By these limitations, the regional forms of this change occurring as part and parcel of local circulatory lesions will not be considered. It will be recognized, of course, that it was these local lesions that gave the original clue to its etiology in an impairment of arterial circulation. This is made clear in a brief survey of the medical history of the lesion.

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The research on which this study is based was made possible by a special grant from the Los Angeles County Chapter of United Cerebral Palsy.

From the Department of Nervous Diseases (Neuropathology), College of Medical Evangelists, and the Cajal Laboratory of Neuropathology, Los Angeles County Hospital.

Historical Introduction

In 1858 S. Weir Mitchell [1] reported an unusual case of a girl who at death, at the age of 13 years, was found to have a widespread laminar degeneration of the cerebral cortex. On gross examination the cortex was marked by a thin horizontal red line, which was considered to be inflammatory in origin. It is not possible to evaluate at this late date the precise cause of this advanced laminar necrosis, as the lesion proved to be on microscopic examination. Nevertheless, it presented a typical defect of the intermediate layers of the cerebral cortex, for it was described as "a cavity whose walls were ill defined [but which] was bounded on all sides by gray matter, and followed the irregular curves of the convolutions."

This lesion then dropped from sight for another 30 years. Then Lissauer [2] described a laminar loss of nerve cells in atypical cases of dementia paralytica, an alteration which he described as *schichtenweise Degeneration*. This observation was verified a few years later by Heilbronner.[3] A similar type of laminar degeneration of the cellular elements was also found by Köppen [4] and Kotschetkowa [5] in the cerebral cortex of idiotic and spastic children. A more pronounced laminar lesion in the form of a layer of vacuolar spaces, a zone of fenestration, was subsequently described by Probst [6] as *Rindenschwund* and by Fischer [7] as *spongiöse Rindenschwund*. Because the basic lesion, laminar loss of nerve cells, was first found

in cases of dementia paralytica with focal cortical softening, it was logically assumed by Fischer [7] that his status spongiosus was likewise of circulatory origin.

Still other terms, such as *Streifenstörung Erkrankungen, Schichterkrankungen, flächenhafte Rindenerweichungen,* or *Rindennekrose,* were soon applied to this lesion, appearing in variable degrees of severity. All of these variants are now included in the designation "laminar cortical necrosis." *

The Essential Problem

This basic lesion seems to be incident to the fact that the nerve cells of the cerebral cortex are arranged in a series of superimposed layers, or laminae. The cells forming these individual strata are quite uniform in size and presumably have a similar function. According to the numerous reports on this lesion now available for study, it would appear that Lamina III, according to Brodmann's classification, is most vulnerable. However, Laminae IV, V, and even VI are not infrequently involved. Indeed, two, or even three, separate laminae may be separately affected and to different degrees.

It is the purpose of this study to review briefly the pertinent literature on the subject, calling attention especially to the various clinical conditions in which it is found. It will be pointed out that there is a close relationship between a laminar loss of nerve cells, at one end of the spectrum, and subtotal cortical necrosis, at the other. The development of the generally accepted concept of its circulatory origin will be noted and its relation to the larger problem of cerebral anoxia stressed. But the primary object of this study is to emphasize the importance of the lesion in an evaluation of this lesion when it is found in the cerebral cortical atrophies in cases of cerebral palsy, mental deficiency, and epilepsy.

Pathology and Pathogenesis of Laminar Cortical Necrosis: Development of Concepts

As has already been pointed out, laminar cortical necrosis was originally recognized as a characteristic architectural alteration in cases of cortical atrophy associated with dementia paralytica (general paresis), as well as in cases of sclerosing cortical atrophy associated with idiocy and palsied states. Lissauer is usually credited with being the first to identify it in cases of dementia paralytica, an observation soon verified by Heilbronner.[3] However, Köppen [4,8,9] also found this same alteration in "congenital" microgyria associated with cerebral palsy, idiocy, and epilepsy. He was perceptive enough to note that this lesion also occurred in cases of arteriosclerosis with related vascular lesions in the cortex. Köppen must therefore be credited with laying a broad foundation for the problem as a whole. His attention, however, was not focused on laminar necrosis as an entity but, rather, was centered on the lesion complex which was associated with what is now known as "nodular cortical atrophy," or "mantle sclerosis," which is to be the subject of another study.

It remained for Fischer [7] to consider laminar necrosis, or, as he designated it, *spongiöse Rindenschwund,* as a specific type of cortical change and to emphasize the frequency of its occurrence in dementia paralytica (12 cases), observations which were to be ably supported later by the studies of Bielschowsky [10] and a number of others. He also described its histological characteristics in greater detail and pointed out that the lesion could be either acute or chronic. Its presence in other chronic cortical diseases was also noted. He failed, however, to consider circulatory disturbance

* There are some who prefer to use the term "pseudolaminar necrosis" to describe this lesion. This seems to be simply begging the question. Whether one views it from a purely morphological standpoint or from the precise group of nerve cells (or their nutrient vessels), the damage, whether cellular or architectural, is based on the specific vulnerability of the cell layers. This seems to be clearly demonstrated in case of experimental anoxia, as well as in the effects of anoxia on the human subject.

as its cause, believing some toxic substance was at work in its production. The subject was further elaborated on in the treatises by Bielschowsky [10] and Spielmeyer.[11] †

The next important contribution to the subject of *spongiöse Rindenschwund* was that by Sträussler and Koskinas.[13] Following the lead of Fischer, these investigators described various stages of the process, noting the important fact that a laminar loss of nerve cells, such as had been observed in dementia precox, senile dementia, and Huntington's chorea, had essentially the same significance as did the more obvious lesion of acute necrosis, presuming that it also represented a vascular effect on the cerebral cortex.

By this time the subject had been given much attention, with respect either to the presence of laminar change in certain conditions or to its incidental mention in others. Particularly important, on one hand, was its frequent occurrence in the cerebral cortex in case of arteriosclerotic vascular disease (Brinkmann,[14] Neubürger [15]), as well as cerebral embolism (Neubürger [16]; Alajouanine, Hornet, and Thurel [17]). It has been observed also in other cases of acute circulatory failure (cardiac standstill under anesthesia, Bodechtel,[18] and profound fall in blood pressure from shock, de Vries [19]). Meanwhile, laminar cortical necrosis had also been observed in asphyxia from exposure to carbon monoxide (Stewart,[20] Hiller,[21] Wilson and Winkelman [22]).‡ It had similarly been seen in asphyxia on a mechanical basis (von Braunmühl [25]).

The accumulating evidence supported the conclusion that laminar necrosis was best accounted for on the basis of an impairment of the cortical circulation to the extent that no other theory is now seriously entertained. Even the attractive and ingenious concept of pathoclysis, as proposed by the Vogts,[26] was considered inadequate to account for it.§

While all features of the problem, i. e., mechanism of laminar necrosis in cases of puerperal eclampsia (von Braunmühl [27]), could not readily be explained on this basis, the group of disorders in which laminar cortical necrosis was found demanded some sort of circulatory disturbance as an explanation (de Vries). This raised the question of the mechanism of ischemia, whether, indeed, vasospasm was possible under so many and varied abnormal physical states. In fact, the question so raised has remained unanswered to the present time.

† Spielmeyer [12] gave special study to focal and laminar loss of nerve cells in Sommer's sector of the cornu ammonis. He found such loss in cases of epilepsy, endarteritis of tuberculous etiology, chronic cortical atrophy, as in Huntington's chorea, and, particularly, asphyxia from carbon monoxide. He believed, as others were coming to do, that this diffuse loss of nerve cells was best explained on a basis of impaired circulation.

‡ To confuse rather than to clarify the issue, laminar as well as focal cell loss had also been observed in certain fatal poisonings other than carbon monoxide. Weimann [23] and others had observed the phenomenon in fatal cases of morphine poisoning, and Spielmeyer [24] had also noted it in the cerebral cortex after lead poisoning. I (Case Studies in Cerebral Anoxia: VI. Typical Anoxic Alterations in the Cerebral Gray Matter After Overdosage of Barbiturates, Bull. Los Angeles Neurol. Soc. 20:16-24, 1955) have found the same alteration after fatal poisoning with barbiturates.

§ In a praiseworthy effort to find some common denominator for the various types of cortical change, including the one here considered, Cecile and Oscar Vogt proposed a theory of specific sensitivity of the nerve cells. They believed that the individual elements of the various cellular laminae were specifically susceptible to various noxious agents and that this explained the laminar loss of such cells under various circumstances. The most serious weakness in their concept lay in their denial that this individual susceptibility had anything to do with the degree of vascularity of the cortex in which the cells resided. In brief, laminar necrosis is more than an inherent susceptibility of a given stratum of nerve cells. It is the result of an impaired circulation of that stratum, whereas the susceptibility of the cell represents an inborn quality of the cell. The mechanics of damage in this case is due to a superimposed factor of selective ischemia. Spielmeyer's treatise (see previous footnote) on specific changes in the cell groups of the hippocampus pointed up this deficiency as well as any purely histological investigation could so do.

Laminar Cortical Necrosis as the Characteristic Lesion in Cerebral Anoxia

The brief survey of the problem of laminar cortical necrosis has served to emphasize the fact that, in general, this characteristic cortical lesion is found most characteristically in cerebral vascular lesions (cerebral embolism, arteriosclerosis, syphilitic vascular diseases, etc.) or conditions in which there is a more or less profound disturbance in the general circulation (prolonged drop in blood pressure incident to shock or cardiac standstill, eclampsia, etc.). In addition, it was noticed that asphyxia incident to exposure to carbon monoxide (Stewart,[20] Hiller,[21] Wilson and Winkelman[22]) was at times also capable of producing the same effect on the cortical gray matter. Asphyxia from mechanical causes and from exposure to the attenuated atmosphere at higher altitudes has resulted in identical lesions. This observation therefore includes asphyxia with other general circulatory disturbances as one of the potent factors in the production of cortical laminar necrosis.

About a quarter of a century ago, when the asphyxiant effects of inhalant anesthetic agents began to be appreciated, several investigators, including me, had the opportunity of studying the delayed residuals of the attendant cerebral anoxia. It was learned that the characteristic cortical changes in the form of focal and laminar necrosis became apparent only if the patient survived for a day or more the anoxic insult.‖ As has been reported at length in several contributions (Courville[28-30]; Löwenberg, Waggoner, and Zbinden[31]; Gebauer and Coleman[32]; O'Brien and Steegmann[33]) on this subject, it was made clear that profound and often extensive laminar cortical necrosis was a characteristic effect of severe degrees of cerebral anoxia under nitrous oxide and other inhalant anesthesias. It was necessary to conclude, therefore, that the outstanding and strikingly characteristic residual effect of cerebral anoxia was laminar cortical necrosis.

The appearance of this lesion as observed in cases of cerebral anoxia of various causes is shown in Figure 1.

Laminar Cortical Necrosis and Cerebral Anoxia.—This conclusion has been abundantly reinforced in my personal experience with the cerebral lesions in other clinical forms of cerebral anoxia.[34] Similar lesions of the cortex have been reported after mechanical suffocation, cardiac standstill under spinal anesthesia, carbon monoxide "poisoning," respiratory failure in bulbar poliomyelitis, and prolonged shock; with hyperinsulinism, drowning, and congenital heart disease, and even after overdosage of barbiturates. This only goes to show that, regardless of the mechanism by which it is accomplished, the effects of anoxemia on the cortical (and ganglionic) gray matter are the same, and that focal and laminar necrosis is the hallmark of these effects.

With such an array of causes of laminar cortical necrosis on an anoxic basis, particularly when one includes those substances supposedly acting as histiotoxic agents (interfering with the utilization of oxygen by individual nerve cells), it may fairly be asked whether, by such a demonstration, one has not raised more questions than he has answered. The fact remains, however, that an understanding of the pathogenesis of cerebral anoxia, particularly that form consequent to nitrous oxide anesthesia, has

‖ At first impression, the separation of laminar cortical necrosis from its commonly associated, and probably antecedent, lesion, focal necrosis in either its acute or its chronic form, seems to be artificial and arbitrary. And yet the fact that this type of disruption of the cortical architecture has been so extensively investigated and described cannot be entirely ignored. But even more important is the significance of the end-stages of the two lesions. Even though one usually finds both lesions present in the brain in many cases of irregular cortical deformation in spastic and mentally defective children, the residual effect of a predominantly focal necrosis is a nodular type of cortical (mantle) sclerosis, while the end-lesion of a predominantly laminar type of necrosis is a diffuse and more or less uniform cortical atrophy. Thus, two quite different series of lesions result.

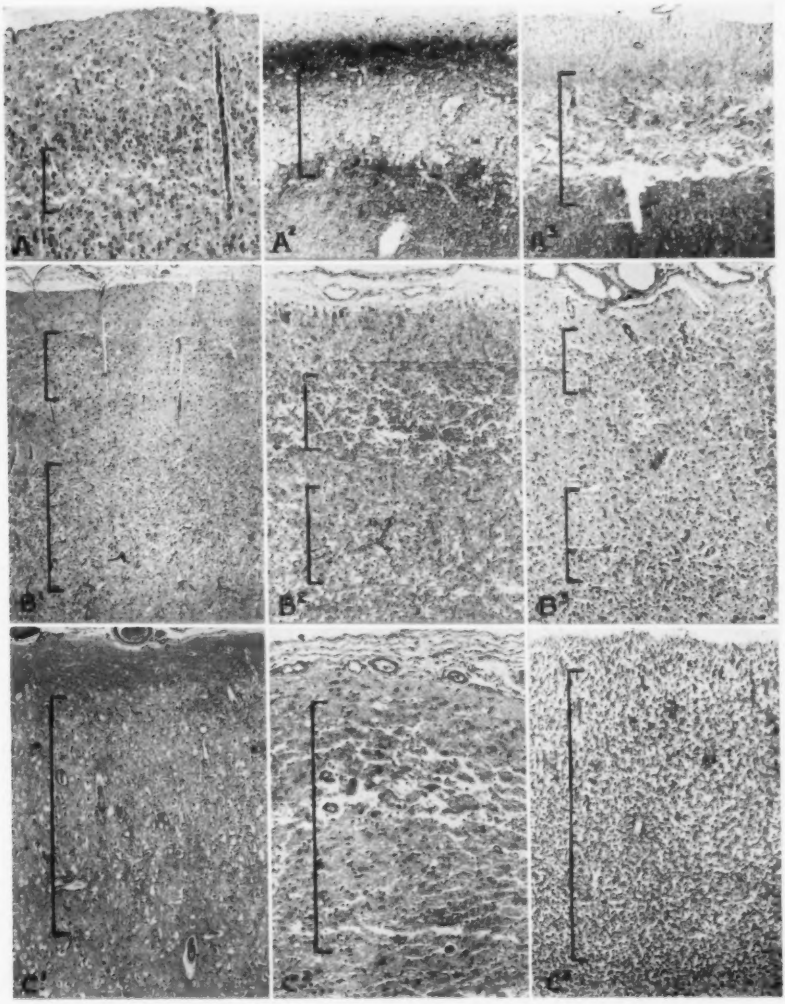


Fig. 1.—Various manifestations of laminar cortical necrosis observed in cases of cerebral anoxia of different etiologies. A^1 to A^3, single zone of necrosis; B^1 to B^3, double zone of necrosis; C^1 to C^3, necrosis of practically all cellular laminae. A^1, minor degree of laminar cortical necrosis in congenital heart disease. Hematoxylin-eosin stain; reduced to 62% of mag. × 188. A^2, early laminar cortical necrosis after nitrous oxide anesthesia. Reduced silver method; reduced to 62% of mag. × 21. A^3, advanced laminar cortical necrosis with formation of glial scar after anoxia under thiopental-nitrous oxide anesthesia. Reduced silver method; reduced to 62% of mag. × 21. B^1, laminar cortical necrosis after mechanical strangulation. Hematoxylin-eosin stain; reduced to 62% of mag. × 27. B^2, laminar cortical necrosis after anoxia incident to cardiac standstill under spinal anesthesia. Hematoxylin-eosin stain; reduced to 62% of mag. × 67. B^3, laminar cortical necrosis after prolonged shock. Hematoxylin-eosin stain; reduced to 62% of mag. × 67. C^1, laminar cortical necrosis after severe hypoglycemia. Hematoxylin-eosin stain; reduced to 62% of mag. × 48. C^2, subtotal cortical necrosis from episode of respiratory failure in bulbar poliomyelitis. Hematoxylin-eosin; reduced to 62% of mag. × 67. C^3, diffuse glial scar involving all cortical laminae as a result of paranatal anoxia. Reduced silver method; reduced to 62% of mag. × 27.

made possible a clearer insight into the problem.

I have been able to formulate some concepts as to the stages in development of the cortical lesions on the basis of my observations in a series of fatal cases of cerebral anoxia under nitrous oxide anesthesia. It appears that in this condition the cortical lesions are remarkably clean-cut, and so well adapted to an investigation of pathogenesis of the cortical lesions (Courville[29]). By grouping these cases on the basis of the length of their survival period, it is possible to develop a reasonably complete picture of the evolution of the lesion. This analysis of the changes resulting in laminar cortical necrosis itself will therefore be but an extension of the earlier efforts in this direction by Fischer and Sträussler and Koskinas.

Pathogenesis of Laminar Necrosis in Cerebral Anoxia.—In my series, the earliest cortical lesion following anoxia as a consequence of nitrous oxide anesthesia was seen after a survival of 37 hours.¶ Under these circumstances, I was able to find small areas of pallor in the intermediate layers of the cortex even under low-power magnifications. With an enlarged view, this pale area is found to be quite sharply circumscribed and to have a typical vacuolated or fenestrated appearance. There is reason to believe that these individual foci represent the area supplied by a small blood vessel. This change results from an enlargement of the pericellular spaces and a shrinkage of their contained nerve cells, as well as from the formation of small vacuolar defects in the interstitial tissues. It is the presence of this conglomeration of spaces which has given rise to the descriptive term "spongy," as used in the early descriptions of the lesion.#

As time goes on, these spaces increase in size, possibly in number as well, until the remnants of the interstitial tissues are compressed into narrow strands, forming a net-like filigree within the focus. The enlarged spaces also outline with greater distinctness the borders of the individual lesions.

With increasing lengths of the survival period, a tendency to a fusion of multiple foci of necrosis becomes evident. Adjacent foci in the same laminae (at times of adjacent laminae as well) enlarge, become confluent, and form a more or less uniform stratum of degenerative change. There can be no question, however, but that with a severer impairment of the laminar circulation, this specifically vulnerable stratum of tissue may disintegrate en masse, so that true laminar necrosis may, in itself, constitute the primary lesion. In other words, laminar necrosis may be the result either of a slower progression by stages or of a sudden, total, and widespread consequence of this anoxic process. These apparent differences are probably to be explained by the speed with which the process occurs rather than by any inherent difference in its mechanism.

The stages of laminar cortical necrosis are shown in Figure 2.

Still another factor in the production of the end-lesion is the degree of anoxic insult to which the affected stratum has been exposed. This is best expressed by the product of severity (s) of the anoxic process by the time interval (t) over which it acted ($s \times t =$ final lesion). This difference can be no better exemplified by the arrangement based on severity of the tissue damage in the final lesions: (1) laminae of cell loss (*Schichterkrankungen*); (2) state of spongy change (*spongiöse Rindenschwund*); (3) state of partial softening with residual vascular scar (*flächenhafte Rindenerweichungen*), or (4) total necrosis with residual defect (*Rindennekrose*).

Keeping the characteristic structural changes and their pathogenesis clearly in view, it is now possible to analyze the rela-

¶ From my correspondence with other students of the problem, I have learned that characteristic changes have been observed as early as 25 hours. It is doubtful that any manifestation of true focal lesions would be found in an interval much shorter than this.

Gildea and Cobb[85] chose to designate these foci with the very descriptive term of "areas of devastation."

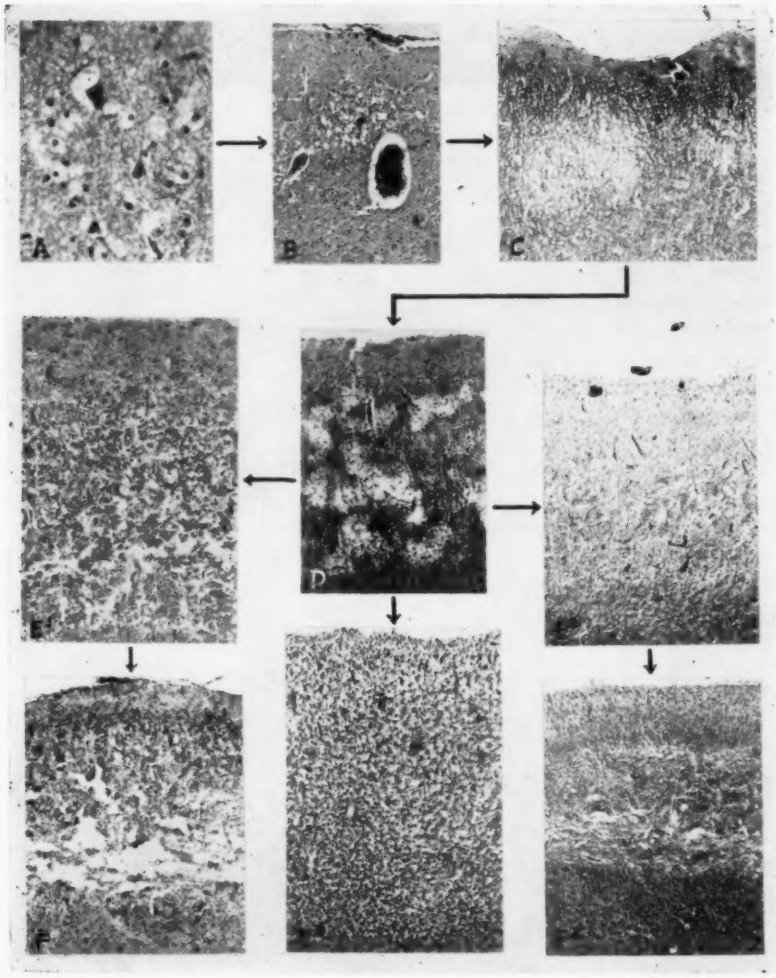


Fig. 2.—Sequence of development of laminar cortical necrosis, showing various stages of process. *A*, early status spongiosus involving local group of nerve cells. Anoxia after nitrous oxide anesthesia. Hematoxylin-eosin stain; reduced to 62% of mag. × 188. *B*, focal status spongiosus in cortex after mechanical strangulation. Hematoxylin-eosin; reduced to 62% of mag. × 39. *C*, fusion of adjacent foci of necrosis as first stage of formation of laminar necrosis. Reduced silver method; reduced to 62% of mag. × 93. *D*, fusion of multiple areas of focal necrosis to form laminar patterns. Bielschowsky silver preparation; reduced to 62% of mag. × 27; F^1, subtotal necrosis in anoxia after nitrous oxide anesthesia. Hematoxylin-eosin stain; reduced to 62% of mag. × 33. E^2, wide zone of cortical necrosis, thiopental-nitrous oxide anesthesia. Reduced silver method; reduced to 62% of mag. × 21. F^2, wide cortical astrovascular scar after anoxia incident to thiopental-nitrous oxide anesthesia. Reduced silver method; reduced to 62% of mag. × 21. E^3, diffuse glial scar involving all cortical laminae as a residual of paranatal anoxia. Reduced silver method; reduced to 62% of mag. × 27.

tionship between anoxemia in general and these purely focal ischemic effects. Both imply the great importance in evaluating the basic circulatory factor essential in the process of laminar necrosis.

Circulatory Component in the Production of Laminar Necrosis

It has long been suspected that some type of circulatory impairment was responsible for the production of laminar necrosis. This theory was based upon the observation that in the majority of the reported cases some disturbance of either the general or the local blood supply seemed to be a common etiological denominator. One of the chief difficulties in the acceptance of this concept was the highly selective destruction of one or more of the cortical cellular laminations, which were quite different lesions from the common local cortical and subcortical softening known to be due to occlusive vascular lesions. A second difficulty has been a lack of understanding of the mechanism of vascular spasm on a vasomotor basis, which mechanism was demanded in view of the fact that no anatomical obstruction could be found.* Finally, no available satisfactory explanation for the laminar arrangement of the lesion was forthcoming, particularly since the pathoclysis theory of the Vogts seemed untenable under the circumstances.

Some of these questions seem to be quite satisfactorily answered by the mechanisms of cerebral anoxia. It now is evident that the particular lamination of cells affected in this disorder is simply more sensitive to oxygen want. With a progressive lowering of oxygen tension in the blood stream, the most vulnerable stratum of cells in certain specific cortical areas (visual and motor cortex) is progressively damaged.

The correctness of this explanation is quite readily appreciated when one compares the stratification of cortical blood supply with the lesion in question. Reference to the work of Pfeifer[36] indicates that the various cellular laminae have their own characteristic capillary bed. In general, it is the intermediate portion of the cortex (Laminae III to VI) which has the richest capillary supply (Fig. 3). It must be assumed, therefore, that the cell layers which demand the most abundant blood supply would be, by analogy, the most sensitive to oxygen want.

This explanation, however, does not account for the incompleteness of destruction observed in even circumscribed cortical areas. It has been commonly observed, for example, that the portion of the laminae in the cortex about the depth of a sulcus is more likely to be damaged than the portion in the crown of a convolution. Moreover, even in fairly extensive laminar necrosis the process is not entirely uniform, particularly at the borders of the lesion. Here, again, we can appeal to the anoxic lesions themselves for a suggested answer.

Focal Necrosis as an Indication of Impaired Blood Supply.—In the case of laminar necrosis one can assume some diffuse deficiency of oxygen supply from any one of the many causes of anoxemia. But focal lesions, areas of necrosis that affect only groups or clusters of cells within a given lamination, can be accounted for only on the basis of some factor acting within the focus. Presuming that all the cells within a given lamina are equally sensitive to a reduction in oxygen tension, if this factor alone were acting, then all cells so influenced should show uniform damage. This presence of a focal circulatory component can be shown in two ways. If sections of cortex in chronic lesions are stained for blood vessels, it is found that the acellular areas are often de-

* The fact that status spongiosus is not infrequently found as a manifestation of a local ischemic process, as well as of a generalized anoxia, cannot be lightly dismissed. Moreover, localized vascular lesions are also found as part and parcel of an anoxemia. This introduces a question which is too comprehensive to be considered in this connection, but will be treated in a second study, concerned with nodular cortical atrophy. Suffice it to say here, laminar loss of nerve cells, status spongiosus, and the severer laminar necrosis are fundamentally due to variable degrees of anoxia, whether generalized or localized, whether anoxemic or ischemic in origin.

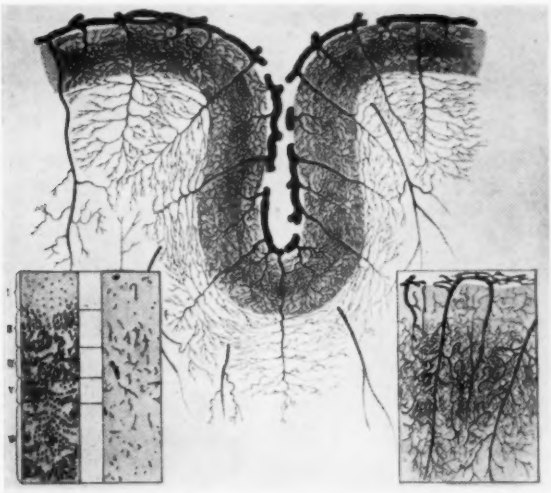


Fig. 3.—Arterial circulation of the cerebral cortex and subcortical white matter (redrawn from Poirier, P. and Charpy, A.: Traité d'anatomie humaine, ed. 3, Paris, 1914). The more abundant capillary blood supply of the intermediate lamina is indicated in the lower right inset (adapted from Pfeifer[20]). Lower left inset shows relation of central laminae (III to V) to zone of densest capillary network (after Craigie, J. Comp. Neurol. 33: 193, 1921).

void of capillary supply. This would suggest permanent occlusion of the nutrient vessel as one possible cause of focal necrosis. In acute cases these foci are often found about dilated venules, suggesting stasis as another factor in producing focal necrosis. Thus, either one or both of two mechanisms, one arteriocapillary, the other venous, may be involved in the process.

In viewing the subject from a wider aspect, the lesion here considered represents only variable degrees of oxygen deficiency as they affect the vulnerable cell layers of the cortex. It matters not whether this deficiency comes from anoxemia of a general nature or whether the shortage in supply comes from a temporary occlusion of the nutrient artery of the areas involved. By reducing below a level of tolerance the amount of oxygen passing through the vessel for a given period of time, physical damage to the individual cells will occur. At a still lower level, the interstitial tissues in the highly vascularized area will also be affected. When the level is lowered still more, partial softening will result. Ultimately, total necrosis of the vulnerable cellular laminae will occur, while the much less sensitive, aneuronic superficial and deep layers of the cortex remain relatively undamaged. With still more advanced degrees of anoxemia not only the more sensitive gray matter but the white matter as well will be damaged, leading to total softening of the cerebral hemispheres.

By way of summary, therefore, it may be said that three major degrees of anoxia are to be considered. The first degree is selective, damaging only the nerve cells or portions of them. The second degree of oxygen want destroys not only the nerve cell but also the interstitial elements, resulting in a total laminar cortical necrosis. The third degree is one sufficiently severe to injure directly the underlying white matter as well as the cortex, resulting in total ablation of those portions of the cerebral hemispheres within range of the deadly process.

Laminar Necrosis in the Uniform Cortical Atrophies of Early Life

A survey of the literature dealing with the gross deforming lesions of the cerebral cortex in early life so commonly associated with the clinical status of cerebral palsy and mental deficiency indicates the frequent occurrence of circumscribed zones of laminar necrosis. The early investigators (i. e., Köppen[4]) called attention to this peculiar spongy appearance of the cortex in the microscopic sections (Fig. 4). From this

Fig. 4.—Laminar cortical necrosis (status spongiosus), as was early noted in sclerosing cortical lesions in cases of cerebral palsy and idiocy. After Köppen (Arch. Psychiat., Vol. 28, 1896, Plate 19, Figs. 6, 9, and 10).

fairly consistent observation, it now seems obvious that this individual type of cortical damage is but one of a cluster of lesions whose sum total constitutes the gross deformations of the brain responsible for these clinical disorders. But, as already stated, the limitations of this subject which have been self-imposed demand that only the occurrence of laminar cortical necrosis as the major, if not the exclusive, alteration present is to be given consideration in this study. In accord with this assumption, one must conclude that any residuals of the process must be in the form of a widespread, more or less uniform cortical atrophy. It becomes necessary, therefore, to select from the larger group of early cerebral deformations such cases as betray this type of atrophy, apparently due directly to a stratified cell loss, spongious necrosis, laminar softening, or subtotal cortical necrosis.

On the basis of the possible lesion pictures, as suggested by the foregoing discussion, the following categories of cases may be distinguished: (1) widespread laminar loss of nerve cells without notable cortical atrophy, usually found in some cases of mental deficiency; (2) widespread uniform cerebral atrophy, total or hemispheral, without local cortical change but with diffuse and laminar nerve-cell loss, usually discovered in cases of cerebral palsy and/or mental deficiency; (3) chronic selective cortical atrophy with replacement gliosis ("walnut-kernel brain"); (4) diffuse progressive degeneration of the cerebral gray matter (Alpers); (5) selective cortical softening with evidence of laminar necrosis still apparent; (6) advanced total cerebral softening with characteristic laminar change noted in the residual cortex; (7) hydrencephaly with status spongiosus, as observed in the small residual masses of gray matter.

"Normal" Brain with Laminar Loss of Cortical Nerve Cells

It is not particularly rare to find a brain which appears to be normal to the unaided eye, both externally and on cut section, in persons who have been palsied or mentally

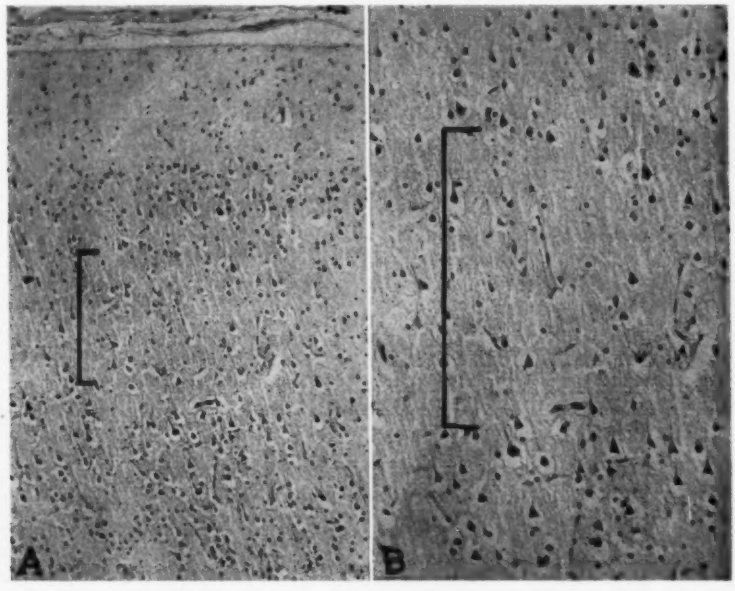
deficient since birth. In such instances, the discovery of a laminar depletion of the nerve-cell population (spotty or patchy cell loss) or an actual laminar defect of cells involving the upper intermediate layers (Laminae III to V particularly) may be forthcoming. One must assume some connection between the clinical deficits, be they motor or intellectual, and this peculiar pattern of cell loss (Rose [37]). This condition is probably not as uncommon as a survey of the literature would suggest, although its exact incidence seems to be unknown.

As an illustration of this type of laminar defect, the *schichtenweise Degeneration* of Lissauer, or the *Schichterkrankung* or *Streifenstörung Erkrankung* of subsequent students of the problem, the following case may be cited.

CASE 1.—This patient, aphasic, mentally defective and epileptic since birth, was a Mexican girl of 17 years at the time of her death. A trephine operation had been done at the age of 6 months, presumably on the diagnosis of a postnatal subdural hematoma. Death resulted from anemia, cachexia, and bronchopneumonia. Aside from a focal adherent leptomeningeal-dural scar at the operative site (right temporal region), the brain appeared to be grossly normal in size and cortical pattern. It weighed 1230 gm. (body weight was only 29.5 kg. [65 lb.]). Microscopically, however, the leptomeninges were found to be moderately thickened. The cortex was marked by areas of both focal and laminar loss of nerve cells (Fig. 5).

In this case the early appearance of mental deficiency presupposes some etiological process occurring during late intrauterine life (after the brain had fully matured), during birth (asphyxia neonatorum), or very shortly thereafter. The mild but rather diffuse laminar loss of nerve cells would further suggest some general circulatory disturbance, such as anoxemia, rather than a focal one. Unfortunately, as is so often the case, the clinical history is silent as to details of any paranatal anoxic episode. Nevertheless, the previous statements as to the pathogenesis of laminar changes in general should lead one to conclude that its genesis must lie in the realm of oxygen want, whatever its mechanism.

Fig. 5 (Case 1).—Laminar loss of nerve cells in normal-sized brain of a mentally defective person. *A*, absence of nerve cells in intermediate layer (Lamina III). Nissl preparation; reduced to 92% of mag. × 40. *B*, enlarged view, indicating faded remnants of pyramidal cells in affected zone. Nissl preparation; reduced to 92% of mag. × 76.



Generalized Cerebral Atrophy with Laminar Loss of Nerve Cells

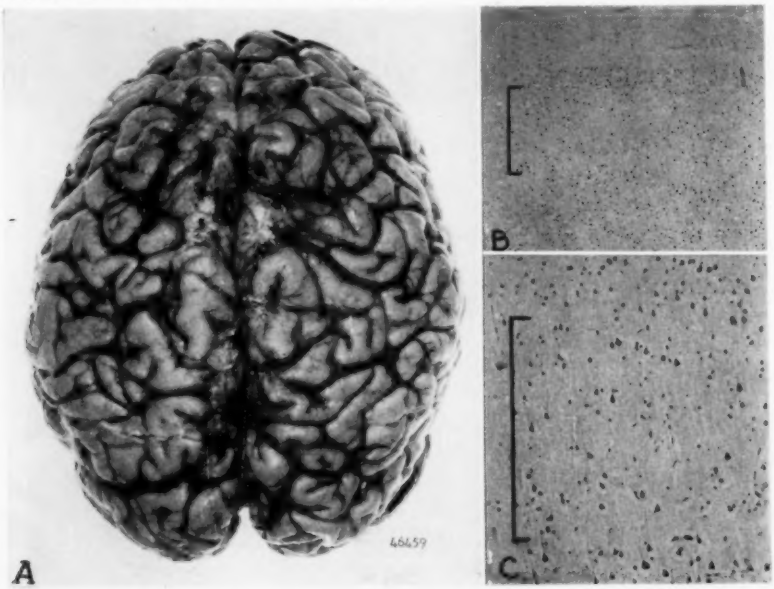
In this second group of cases, the initial noxious process is obviously somewhat severer, so as to result in diffuse damage to the brain to a degree to make the atrophy evident to the unaided eye. The brain in these cases is definitely smaller than average for a normal person of the size and age of the patient. This may also be noted in a comparison of the weight and fluid displacement of the cerebrum and cerebellum.

An example of this group of diffuse lesions is to be found in the following brief case report.

CASE 2.—A white adolescent youth, aged 14, died of confluent bronchopneumonia. His mother had been in labor for three days prior to his birth. Convulsions developed at the age of 3 months and persisted throughout his life. He was seriously retarded mentally and was paraplegic. The brain, which was grossly unaltered as far as focal cortical lesions were concerned, weighed 1120 gm. The cerebral hemispheres were equally atrophic, and the cortex felt firm to palpation. The individual convolutions showed a mild degree of atrophic change, but no true microgyria was evident (Fig. 6*A*). Microscopic examination disclosed a laminar loss of nerve cells, a process which still seemed to be progressing (Fig. 6*B*). Within the zone of cell loss, under higher magnifications, deterioration of individual cells seemed to be taking place (Fig. 6*C*).

In this instance, epilepsy, mental deficiency, and spasticity with paraplegia (Little's disease) followed a difficult delivery. After death from intercurrent pneumonia, the brain was found to be only slightly atrophic, with only a minor degree of shrinkage of the individual convolutions. The loss of nerve cells was apparently diffuse, but more marked in the superficial cell layers. In the lateral aspects of the smaller gyri a definite laminar deficit could be made out. As to etiology, one can only assume that some generalized circulatory disturbance, probably in the form of an anoxemia, had taken place at the time of birth. This was of a degree sufficient to destroy many of the cortical nerve cells, particularly in the upper cortical laminae.

Fig. 6 (Case 2).—Laminar cell loss in the cortex of a spastic, epileptic, and mentally deficient child with only moderate cerebral atrophy. *A*, dorsal view of brain, showing only minor atrophy of individual convolutions. *B*, laminar loss of nerve cells. Nissl preparation; reduced to 69.5% of mag. × 28. *C*, higher magnification, showing changes in individual cells. Nissl preparation; reduced to 69.5% of mag. × 80.



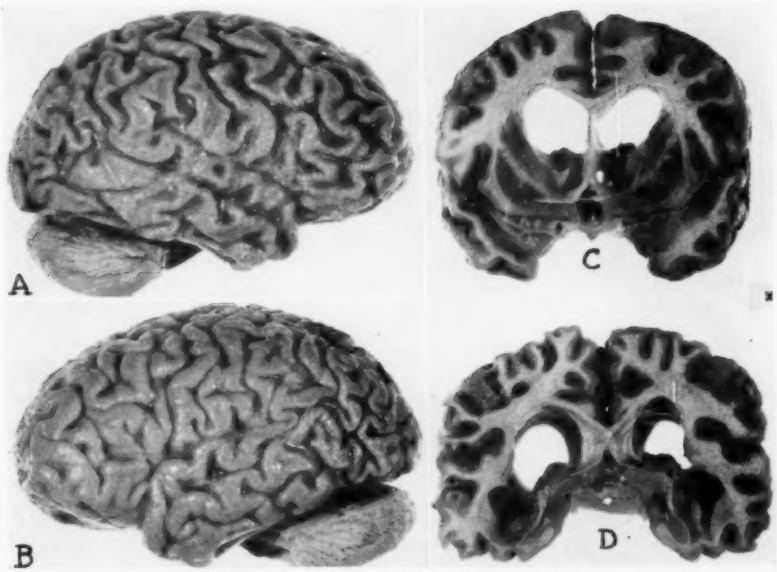


Fig. 7 (Case 3).—"Walnut-kernel" brain. Note marked uniform shrinkage of convolutions of dorsolateral surface of entire right hemisphere (*A*) and inferior and posterior portions of left hemisphere (*B*). Cross sections of the cerebral hemispheres (*C* and *D*) show fairly uniform cortical atrophy, differing in degree on the two sides. See Figure 8 for microscopic cortical changes.

"Walnut-Kernel" Brain

In this group of cases, with diffuse and fairly advanced cortical atrophy, the descriptive name of "walnut-kernel" brain may be used. As the name implies, the cortical atrophy is quite profound and associated with gliosis, giving the narrowed convolutional ridges a sharply outlined, firm contour, much like the projections of a walnut meat. This lesion is obviously one of slower evolution. The distribution of this change may vary considerably, at times involving most of the brain; at others one hemisphere or portions of both hemispheres may be affected. In the last instance, the distribution of the atrophic change usually follows quite closely the area supplied by one or more of the major cerebral arteries. Microscopically, the loss of parenchymatous elements follows a laminar pattern, although true necrosis may not be present. These facts suggest a moderate degree of ischemia within one or more major arterial fields, the cause of which is often not immediately apparent. In other cases, however, the cortical alterations are quite as widespread as they are uniform.

The following brief report of a case will serve to identify the lesion.

Case 3.—The patient in question was a four-year-old girl, born with the aid of forceps after a normal pregnancy and a labor of 10 hours. The child appeared to be normal until the age of 3½ years, when convulsive seizures appeared, followed by progressive aphasia, spastic quadriplegia, and mental deterioration, associated with marked emaciation. The convolutions of the brain were markedly atrophic, separated by greatly widened sulci. They were quite firm to the touch. The areas of the cortex supplied by the right middle and posterior cerebral arteries and the left posterior cerebral artery seemed most affected by the process (Fig. 7). On microscopic examination, it was found that the thickness of the cortex was, in general, directly proportional to the number of nerve cells present. In the areas where only a few cells were present, the cortex had a fenestrated appearance (status spongiosus), and such areas presented a dense overgrowth of glial fibers (Fig. 8). This scar often conformed to a laminar pattern. Many of the cerebellar folia were also

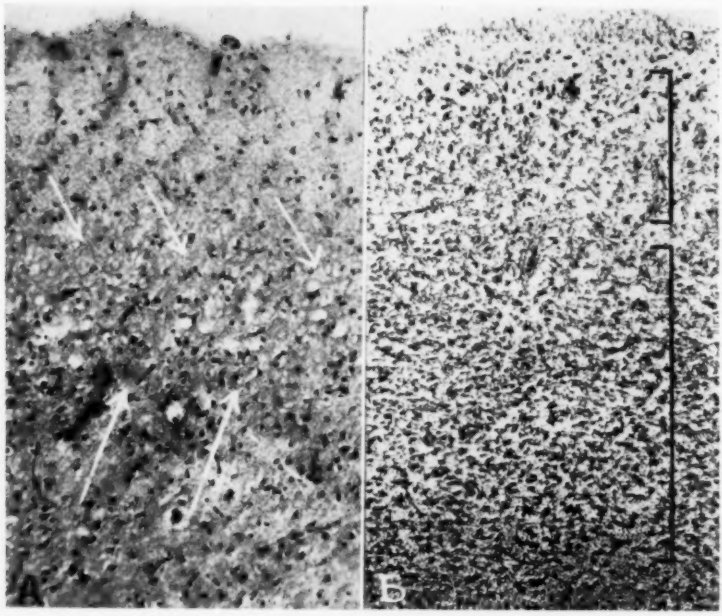


Fig. 8 (Case 3).—Uniform widespread atrophy of the cerebral cortex. *A*, absence of nerve cells with some status spongiosus (arrows). Hematoxylin-eosin; reduced to 92.5% of mag. × 108. *B*, replacement gliosis showing wide band of scar involving all cortical laminae. Reduced silver method; reduced to 92.5% of mag. × 60.

atrophic, with a reduction in the Purkinje cells and at times also of the granule cells.

To add interest to the problem was the history of beginning symptoms of a similar character in a sister one year younger than the patient. The cause of the cerebral (and cerebellar) lesion seems to be very definitely associated with an impairment of the cerebral circulation. This is suggested not only by the distribution of the cortical atrophy but also by the nature of the process (status spongiosus and laminar scarring). But what precipitated or prolonged the ischemic process was unknown.

Diffuse Progressive Degeneration of the Cerebral Gray Matter

Under this title Alpers[38] described a diffuse lesion of the cerebral cortex characterized by necrotic changes associated with a remarkable loss of nerve cells in Lamina III. In some of these necrotic zones early softening with proliferation of the capillary endothelium was evident. The cortical changes were associated with areas of focal necrosis in the globus pallidus, the thalamus, and the pons. This situation seemed to be exemplary of a definite, but rare, complex, for several other cases following a similar pattern have since been reported. Alpers cited the case of Somoza; and since the publication of his paper additional instances have been described by Freedom,[39] Ford,[40] and Christensen and Krabbe.[41] Löwenberg, Berlin, and Luros[42] reported four cases which seem to fit into this category, although considerable variation in the degree and extent of damage in the cerebral gray matter was noted. One of the three verified cases (Case 2) of widespread cortical necrosis described by Ford, Livingston, and Pryles,[43] would seem to fall in this category, the other two showing a difference in degree of cor-

tical changes found in the two hemispheres.† The lesion is usually found in infants but has also been reported in older persons (Freedom, Löwenberg et al.). No consistent etiological factors have been elicited, although in Somoza's case there was a definite history of asphyxia at birth, and in the cases reported by Löwenberg et al.[42] and Ford et al.[43] difficulty in labor was noted. The significant pathological picture in all cases is a widespread laminar cortical necrosis, involving especially the vulnerable third layer. The diffuse character of this laminar type of necrosis definitely includes it in the general group of cases here being considered. In the infant group, some anoxemic or oligemic process is to be suspected; in the older children, some profound circulatory disturbance, possibly precipitated by an infectious process, seems to be responsible.

What seems to be a fairly typical case of this disorder which has come under my scrutiny will be briefly described.

Case 4.—An infant of 4 months, spastic and epileptic since birth, with associated cyanosis and dyspnea, and having a thrill and murmur over the cardiac apex, indicative of congenital heart disease, died of bronchopneumonia. At autopsy, the head and brain (weight, 340 gm.) appeared to be smaller than average. An intraventricular septal defect and patent ductus arteriosus were also disclosed. Palpation of the cortex of the cerebral hemispheres disclosed a variable degree of softening, although in some areas (central and uncinate gyri) it was of normal texture. On horizontal section, the cortex seemed structurally altered and thinned, and in some areas was associated with foci of subcortical softening (Fig. 9*A*). Microscopic examination revealed an almost universal laminar necrosis involving the intermediate zone. This varied considerably in degree, being manifest in some sections by loss of nerve cells; in others total destruction had taken place, so that the leptomeninges and the superficial zone of the cortex were totally separated from the deep layers (Fig. 9*B* to *E*). A reactive gliosis had taken place in the underlying white matter.

The brain in this case presented two lesions, undoubtedly closely associated. On horizontal section of the cerebrum the cortical changes were not particularly striking. There were, however, a number of foci of softening of the subcortical white matter which were quite obvious. These foci presumably represented the end-result of an impaired regional circulation, which, in turn, was evidently part of a widespread process affecting the entire brain. In this case, the cause seems obvious—a congenitally defective heart with a serious impairment of the general and cerebral circulation. The history of asphyxia at birth in Somoza's case suggests that this may be another mechanism capable of production of the lesion. But these known causes of the process are sufficient to include this disorder among those due to seriously impaired oxygenation of the brain.

Selective Cortical Softening

This group of cases may be considered but an advanced degree of laminar cortical necrosis as compared with the lesion found in the cases of diffuse progressive degeneration of the cerebral gray matter just considered. It is a grossly obvious rather than a microscopic lesion, a subtotal destruction of the cortex, in contrast to the microscopic laminar necrosis. The white centrum seems to be only secondarily affected. This alteration likewise appears to be one which results from an impairment of oxygen supply (at times through a deficiency of the cerebral circulation) to a degree in which the cortex is grossly and profoundly damaged but which does not affect the underlying centrum. Cases at this precise level are evidently quite rare, I not having had the opportunity to study one.

Unilateral or Symmetrical Distribution of Selective Cortical Softening.—From the few reported cases it would appear that the cortical lesions which are limited to one

† This variation in the degree of laminar necrosis, as well as the extent of cortical and ganglionic involvement per se, emphasizes the point which I am trying to stress in this study. They suggest that it is possible to cite an example for almost every possible stage in the process of breakdown, from laminar cell loss to total cortical necrosis. In other words, the underlying process must be recognized and stressed, rather than waste time attempting to establish a new category for every stage in this progressive cortical deterioration.

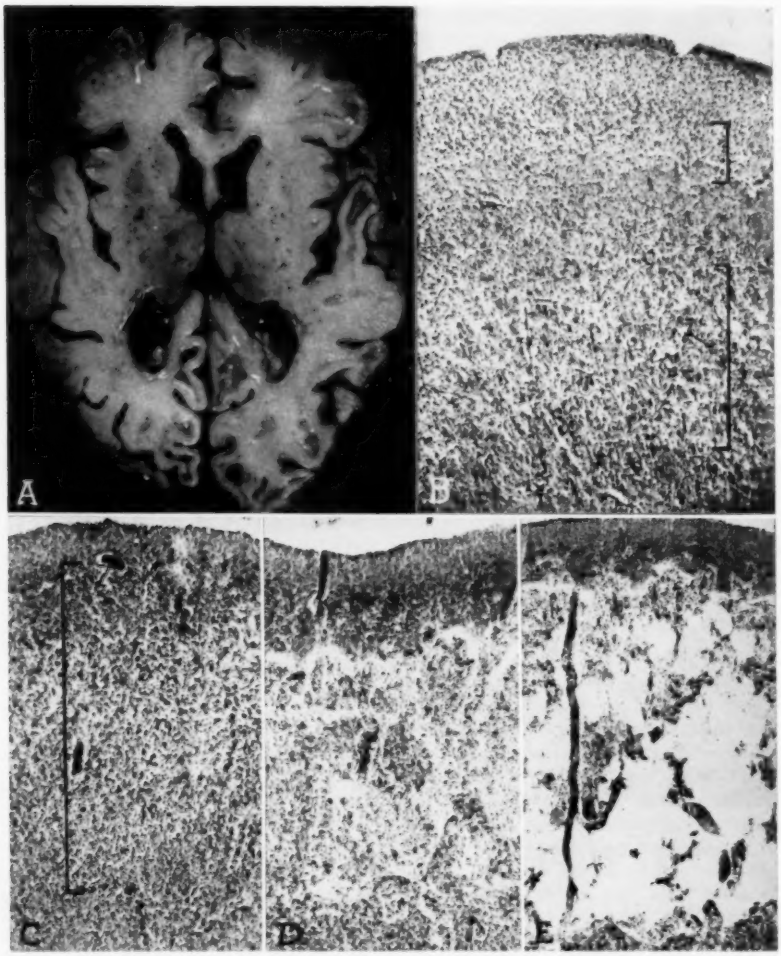


Fig. 9 (Case 4).—Diffuse progressive degeneration of the cerebral gray matter (Alpers[28]). *A*, horizontal section of cerebral hemispheres showing granular appearance of cortex and presence of subcortical and central foci of softening. *B* to *E*, photomicrographs showing different degrees of wide laminar necrosis. All by reduced silver method; reduced to 65% of mag. × 42.

cerebral hemisphere (Siegmund,[44] Stroh,[45] and Hallervorden[46]) present the most typical lesions in this case. In the case reported by Stroh, for example, the cortex of the left cerebral hemisphere was severely damaged, appearing like a layer of yellowish granular debris over a relatively intact cerebral centrum. In Levin's case[47] the cortex of both parietal lobes was similarly altered. These regional lesions obviously imply intervention of an ischemic factor and serve again to stress the identity of anoxemia and ischemia insofar as the end-results are concerned.

In all cases, whether the cortical change is general, hemispheral, or localized, the basic factors seem to be much the same. The lesion occurs most frequently in the first year of life. It evidently results in profound motor phenomena, both convulsive and paralytic. It is essentially a case of cerebral decortication, sometimes partial, sometimes complete. The exact cause of the

condition is uncertain, although its occurrence in early life, without other interposed factors, again points to some untoward experience at birth.

Advanced Total Cerebral Softening

Thus far in this series of lesions, the essential anoxic damage has been confined to the cerebral gray matter, with the cortical component conforming to a laminar pattern. Any damage to the underlying white centrum was essentially secondary. But if oxygen want progresses to a still severer degree, the white substance is also damaged, and changes indicative of complete ischemia are forthcoming.

Again, a series of cases have been reported which seem to suggest this definite lower level of cerebral damage. These cases also seem to be predominantly those of infants within the first few months of life. The brain is reduced largely to necrotic debris, only remnants of cortical tissue remaining. Unfortunately, some of those actually reported (i. e., Sutherland and Paterson [48]) are inadequately described, so as to leave one in some doubt as to their exact classification. The case of Thomson and Piney,[49] however, seems to be quite typical of this condition. In Dahlmann's case [50] of a 58-day-old infant, the degree of involvement of the left hemisphere was not so marked as was evident in the right, but the brain as a whole was reduced simply to a "bag of mush." In the case reported by Edinger and Fischer,[51] the brain presented much the same appearance.‡ In Meier's case,[52] the infant attained the age of 5 months; both hemispheres were totally softened. Schob [53] described essentially an identical lesion in an infant of 2 months. Jakob [54,55] reported two cases with total softening of the brain, including cortex, centrum, and basal ganglia. In Wohlwill's case [56] the infant was only 7 weeks old.

‡ Edinger and Fischer introduced a clinical term to describe these infants, "child without brain," which has been used by a number of observers since to indicate a living human being without cerebral hemispheres.

I have studied a similar case in a premature infant who survived only 5 weeks.

Case 5.—The brain was that of a premature Negro male infant who survived his birth only five weeks. Because of large bullous lesions of the skin, a clinical diagnosis of erythema multiforme bullosum had been made. The entire brain, cerebrum, and cerebellum were reduced in size, and the pallium was remarkably thin. The cortical markings could still be made out, for the external layers of the cortex were intact. The collapsed state of the hemispheres, however, resulted in a wrinkled appearance of the surface of the cerebral hemispheres (Fig. 10*A*). The basal ganglia (corpus striatum and thalamus) were small but presented a normal anatomic conformation. The ventricles were passively enlarged. The brain stem and cerebellum were also small but morphologically intact. The internal carotid arteries were diminutive but appeared to be patent. On microscopic section, the cortex was seen to be totally degenerated, the stroma being filled with macrophages and marked by a general pattern of laminar necrosis (Fig. 10*B*).

The most striking point of interest in this and similar cases is, of course, the obvious circulatory basis for such a profound destruction of brain tissue, practically the entire cerebrum being involved in this instance. The circulatory deficit is represented in this case by a marked reduction in size of the carotid arteries, possibly of congenital origin. In the remnants of tissue, evidence of a laminar pattern of degeneration was disclosed. Thus, like the grin of the famed Cheshire cat, it not only is the striking feature in the intact brain but also constitutes the only aspect of the lesion which persists as long as any recognizable tissue remains.

Hydrencephaly

Little needs to be said about this, the most advanced lesion of the series. Hydrencephaly is obviously the result of total destruction of the nervous tissues, with removal of the resultant debris. Small remnants of cortical gray matter may be found in the membranous sac which constitutes the gross lesion. It has been suspected that arterial obstruction was the cause of this profound loss of nervous tissues (Lange-Cossack [57]). This theory seems to be convincingly proved by Becker,[58] who produced a characteristic

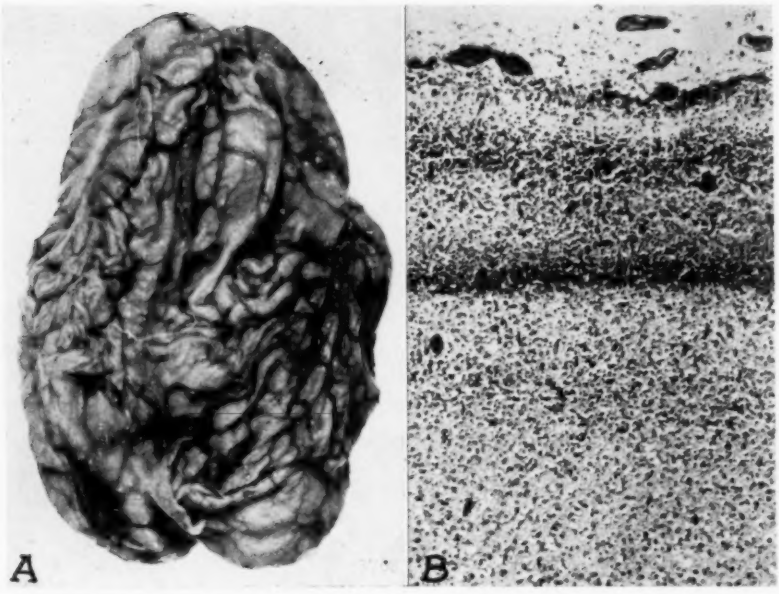
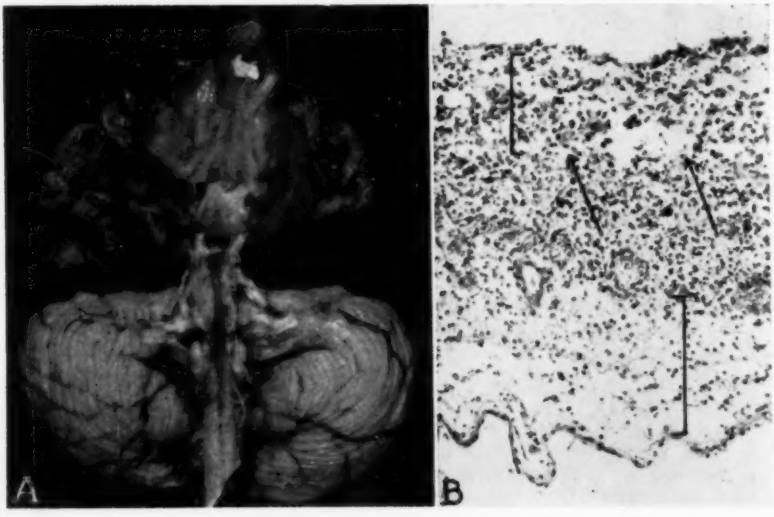


Fig. 10 (Case 5).—Total cerebral softening in a 7-month-old infant. *A*, dorsal view showing characteristic wrinkled appearance of cerebral surface. B, photomicrograph of laminated appearance of cortex. Hematoxylin-eosin; reduced to 86% of mag. × 75.

Fig. 11 (Case 6).—Hydrencephaly. Cerebral hemispheres are reduced to a bag of fluid (*A*), with only small remnants of cortical tissue. In these remnants, the pattern of laminar degeneration is still traceable in the looseness of the upper layer (arrows) of the cortex. The white matter is here represented by a loose network of glial fibers, in which fat-laden macrophages are found. Hematoxylin-eosin stain; reduced to 67% of mag. × 100.



lesion in young animals by injecting particulate matter into their carotid arteries.

A brief case report will make the nature of the lesion clear.

CASE 6.—A girl of 4 years had been born after a prolonged labor of 48 hours, but with postnatal symptoms. Quadriplegia with spasticity, amentia, and absence of visual or auditory sensation became apparent with the passage of time. Sacs of fluid were found at autopsy to have replaced the cerebral hemispheres, with almost total absence of cortex and centrum (Fig. 11*A*). Small nodulations at the base alone represented the basal ganglia, the cerebellum and brain stem being intact. Microscopically, only glial cells were found in cortical remnants with suggestion of laminar necrosis. The superficial layers of the cortex were represented by a spongy network of tissue of glial origin. The deeper layers were somewhat denser. The remnants of a few iron-encrusted cells were seen. The white matter was represented by a loose areolar tissue in which compound granular corpuscles could still be seen (Fig. 11*B*).

In this instance, a thin stratum of residual cortex was found microscopically, lying beneath the thickened arachnoid. This proved to be only the superficial layer of the cortex devoid of nerve cells. What was originally the intermediate cortex, containing the cellular laminae, was reduced to a zone of debris, with deposit of calcium and/or iron in many of the degenerated nerve cells.

A series of cases of hydrencephaly in which the residual tissues have been studied both grossly and microscopically in the Cajal Laboratory show almost every gradation between total cerebral softening, constituting the previous group of cases, and the type of ultimate lesion in which only the leptomeninges and fragments of the ependyma remain.

It thus appears that a genuine hierarchy of laminar cortical lesions is to be found in infancy and childhood, ranging from a selective laminar loss of cortical nerve cells, on one hand, to almost total destruction of the brain mass, on the other. A comparison of the degrees of oxygen want and the resulting pathological state in this series of cases is indicated in the accompanying Table. A laminar arrangement of the residual tissues in all of these cases, be they little or large in amount, betrays the occurrence of an ischemic process at work, regardless of what the original cause may have been. Thus, the mechanism of anoxia, whether initiated by anoxemia, a general process, or an ischemia of secondary development, is found to be the basis of all lesions in this series of entities. If all the reported cases in this series were available for classification, it is very likely that every gradation between the various type cases here cited would be found. There seem to be, nevertheless, certain characteristic stages which have come to be recognized, as depicted in the various series of cases here briefly reported. Further ex-

Comparison of Grades of Anoxia in Production of Widespread Uniform Cerebral Atrophies of Early Life

Degree of Anoxia	Grade and Definition	Residual Lesion
1° Selective damage to nerve cells	Grade A: Selective injury to nerve cells most vulnerable at time of insult	Patchy loss of nerve cells with ultimate general cerebral atrophy *
	Grade B: Selective damage to nerve cells in most vulnerable lamina, especially lamina III (Cases 1 and 2)	Laminar loss of nerve cells with ultimate general cerebral atrophy †
	Grade C: Selective damage to all cortical nerve cells involving all laminae (Case 3)	Diffuse loss of parenchymatous elements with replacement gliosis ("walnut-kernel" brain)
2° Selective damage to cortical gray matter ‡	Grade A: Damage of both nerve cells and interstitial elements in most vulnerable laminae (Case 4)	Diffuse progressive degeneration of cortical gray matter (Alpers)
	Grade B: Diffuse damage to all elements of all laminae	Example resulting from paranatal anoxia not yet seen; fairly common in adult life
	Grade C: Destruction of entire gray cortex	Selective cortical necrosis
3° Damage to both gray and white matter	Grade A: Mild diffuse cortical and central degeneration	Not yet reported in early life
	Grade B: Early softening of both gray and white matter (Case 5)	Subtotal necrosis of brain ("infants without brain")
	Grade C: Total disappearance of gray and white matter (Case 6)	Hydrencephaly

* This patchy loss of cells is not a feature of the present problem and is not considered in this connection.

† Cerebral atrophy is general in the milder, less rapidly progressive cases. Conspicuous cortical atrophy becomes evident in the severer and more rapidly evolving lesions.

‡ In cerebral anoxia coincident damage to the basal ganglia, less often of the brain stem, is also to be anticipated. These associated ganglionic findings are here ignored as outside the subject of this thesis.

perience and more critical observation will doubtless add to our knowledge of the interval lesion complexes.

Although the lesions here described, especially in their more profound state, are not very common, an understanding of the mechanisms involved in their production is of considerable importance in the evaluation of the causative factors. Evaluation of these etiological factors is the next, and final, step in the development of this concept on the etiology and pathogenesis of laminar change.

Primary Etiological Factors in Production of Laminar Necrosis in the Widespread Cortical Atrophies of Early Life

To say that the presence of laminar necrosis in these widespread and often advanced cortical atrophies of early life indicates the intervention of some circulatory disturbance is nothing new. Almost from the beginning of the investigation of this lesion, the intercurrence of some circulatory component has been suspected. Even in the case of this group of severe cerebral atrophies in idiotic, spastic, and epileptic children, the occurrence of some impairment of circulation as an etiological factor has likewise come to be accepted as factual (Benda [59]).

There yet remains the question: "What is the underlying cause of this disturbance in circulation, so profound and prolonged as to produce such crippling lesions of the brain?" No satisfactory answer to this question has hitherto been suggested, one which could explain adequately those lesions which of necessity date back to birth. There are not many pathological conditions which could affect the vessels of the brain of the fetus in utero with resulting oligemia (reduction in blood volume), particularly now that congenital syphilis has become uncommon.

The chief incriminating factor reported in many of these cases is that of a difficult delivery from any one or more of a dozen causes. And so "birth injury" has been considered to be the responsible causative mechanism. But an answer to the question as to what the precise traumatic mechanism of this necessary circulatory change really is has not been forthcoming. Some, it is true, have tried to account for some of these lesions on the basis of thrombosis of the venous channels, especially of the veins constituting the internal system of Galen. The very nature of the cortical lesion in question, laminar cell loss or necrosis, demands an arterial, rather than a venous, component in its etiology.

The time has now come to investigate the situation from quite another viewpoint, that of paranatal asphyxia, to determine whether or not a better basis can be established for the etiology and pathogenesis of laminar cortical necrosis. A precise definition of terms is first in order.

Paranatal Asphyxia vs. *Birth Injury.*—Physicians have long been accustomed to laying at the door of "birth injury" almost every abnormal state that dates back to a difficult delivery. Usually no distinction is made between the true traumatic aspects of such deliveries and the attendant asphyxiant manifestations. It is important to know that true traumatic intracranial lesions of the brain proper following delivery in infants who survive for any extended period are relatively few in number. These lesions include tears in the falx cerebri and tentorium (without clinical significance in themselves), focal scars from depressed fractures, and hemorrhage. As for the last, and most significant, lesion, the effusion of blood may be subdural, subarachnoid, intracerebral, or intraventricular. Subdural hemorrhage, if severe, is immediately fatal; otherwise, a subdural hematoma develops which is relatively rare, having its own characteristic residual syndrome. Subarachnoid hemorrhage is quite common but rarely of any clinical or pathological significance, either immediately after birth or later. Intracerebral hemorrhages, if at all severe, are likewise fatal. Otherwise, little by way of

residuals is to be expected. If bleeding into the intraventricular spaces does not cause obstruction of the cerebral aqueduct or result in the formation of adhesions about the exits of the fourth ventricle, with resultant internal hydrocephalus, it is probably innocuous. Thrombosis of the venous system, either external or internal, as a direct result of delivery seems to be extremely rare. Moreover, occlusive arterial lesions as a direct consequence of delivery are practically unheard of.

It must be concluded, therefore, that the chief significance of the traumatic factor in delivery is the production of increased intracranial pressure in the fetus, resulting in respiratory irregularities leading to apnea. To this end, excessive narcosis of the mother contributes greatly (Courville [60]).

There remains for brief investigation the possible relation of paranatal asphyxia to these circulatory troubles which seem to be at the basis of laminar necrosis and allied cortical lesions. Are there any known mechanisms in cerebral anoxia which may be responsible for significant circulatory changes? Brief reference to a few fundamental principles regarding the relation to circulatory changes in cases of cerebral anoxia will be helpful.

1. There always exists a close relationship between the general and the intracranial circulation in severe degrees of anoxemia.

2. Acute anoxemia is always accompanied by profound disturbances in the cerebral as well as the systemic circulation in the form of marked congestion and focal hemorrhage.

3. There is reason to believe that, as a part of the anoxic state, serious disturbances in both the arterial (vasoconstriction) and the venous (dilatation and stasis) circulation are prone to occur as a significant part of the anoxic process.

4. The occurrence of selective damage to the cerebral cortex in the form of focal and laminar changes indicates the intervention of some purely regional vascular component which localizes and intensifies the universal action of oxygen want.

5. This arterial effect not only is manifest at the cortical level but also causes transitory occlusion, presumably by vasoconstriction, of regional arteries.

6. Experimental studies also show that paranatal anoxia can influence selectively the circulation of a given cerebral lobe or one cerebral hemisphere (Windle, Becker, and Weil [61]).

7. Circulatory disturbances may continue to be present for some time after the acute asphyxial episode is passed, prolonging and accentuating the original anoxic effects on the vulnerable gray matter.

In contrast to the purely mechanical effects of difficult delivery are those which are due specifically to oxygen want, whether acute and clearly evident or minor and prolonged. As is obvious in fatal cases of cerebral anoxia of later life, these primary anoxemic effects are capable of setting in motion vasomotor disturbances which can either result in total ischemia of a given region (with cortical-subcortical softening) or exert a more selective effect on the vulnerable intermediate laminae of the cerebral cortex. This seems to be demonstrated beyond equivocation by the production of a classical status spongiosus, either as a result of transitory occlusion (vasospasm) of a regional artery (ischemia) or by generalized deficiency of oxygen in the blood stream (anoxemia). The local ischemic component which also plays such an important role in the production of the causative lesions of mental deficiency, cerebral palsy, and epilepsy will be considered in a second study.

The coincidence of the purely focal lesions of laminar necrosis (status spongiosus) and the widespread cortical atrophy in this group of grossly deforming lesions of the brain suggests that many of them have their genesis in asphyxia at the time of birth. This is not to say that, in individual cases, functional or structural vascular disease may not be the exciting cause of similar localized lesions. But when a diffuse atrophic change in the cerebrum is also present, anoxemia is the more likely cause, one which sets the

stage for the essential mechanism (vasomotor disorders with ischemia) that accounts for the total picture.

Summary and Conclusions

Laminar cortical necrosis in its various architectural forms (including status spongiosus) has long been recognized as one of the typical cerebral responses to disease processes. It was early recognized to be a characteristic element in the lesion complexes in the widespread, and often profound, cortical atrophies found in spastic and mentally defective infants and children, as well as in a number of diseases of later life.

This type of cortical change in infancy is found to be but one of a hierarchy of lesions which include a laminar loss of cortical nerve cells, true status spongiosus, laminar cortical softening with formation of a vascular scar, one or more laminae of necrosis, and subtotal cortical necrosis.

This characteristic lesion may occur either as a local change in consequence of ischemia in older persons, apparently resulting from a transitory or an incomplete arterial occlusion (vasospasm, incomplete thrombosis), or as a result of anoxemia, occurring either in infancy or in later life, when the cortical alterations are widespread. When a result of paranatal anoxia, the anoxemia itself seems to be the factor responsible for initiating the secondary cortical circulatory disturbances. This observation establishes the primary, or essential, cause of this lesion as a lack of oxygen. Laminar necrosis will develop under appropriate circumstances, regardless of the precise mechanism by which the amount of oxygen reaching the affected area is reduced.

The peculiar laminar arrangement of cell loss or necrosis is due to the selective vulnerability of the affected strata of cortical nerve cells, which is proportional to the richness of its capillary blood supply.

The occurrence of any form of laminar cortical necrosis (i. e., status spongiosus), either as an element in general circulatory disorders or as focal ischemic lesions of the brain, is dependent upon a lessened blood (and hence oxygen) supply. Attendant vascular disease (syphilis, arteriosclerosis) or vasospasm (embolism) accounts for this change in the cortex bordering such focal destructive cerebral lesions.

In the gross deforming lesions of the brain (mantle sclerosis and cyst formation) found in spastic or mentally defective infants and children, laminar cortical necrosis constitutes but one of a group of lesions making up the total picture. On the other hand, this change may prove to be the chief alteration resulting in a diffuse, widespread, and quite uniform cortical atrophy. The several degrees of cortical damage which characterize the resulting lesions make up a veritable hierarchy of these laminated atrophic defects.

Profound or persistent abnormal circulatory states in utero (oligemia) or paranatal asphyxia, rather than isolated and secondary postnatal vascular lesions, probably account for the majority of this group of disorders of early life. The general anoxemic state produces a vasomotor instability which not only prolongs the state of oxygen want but also focalizes it either to limited areas (nodular atrophy) or to specific cortical strata (laminar necrosis, status spongiosus), which are often associated with diffuse uniform atrophy of the cerebral cortex.

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Effects of Induced Hyperthermia on Some Neurological Diseases

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Several authors have reported that induced hyperthermia causes the development of neurological changes in patients with multiple sclerosis. Collins [1] reported that one patient developed flaccid paralysis of all extremities and anesthesia below T-12 while receiving fever therapy. Others of his patients developed an intensification of nystagmus. Guthrie [2] performed hot-water immersion studies on patients with multiple sclerosis and found that they experienced weakness, dysarthria, diminished visual acuity, and scotomata when they were totally or partially immersed. These signs would also appear when only one extremity was immersed, and their appearance could be prevented by applying an arterial tourniquet to the immersed extremity. Edmund and Fog [3] exposed 45 patients with multiple sclerosis to an air temperature of 131-149 F, and confirmed Guthrie's observations concerning weakness and diminished visual acuity. Although they were unable to observe the development of a central scotoma, they did observe exacerbations of nystagmus and changes in the extraocular movements, such as ptosis and "rectus muscle palsy." With the exception of generalized weakness during exposure to heat, these other manifestations of nervous system dysfunction during hyperthermia have not been reported as occurring in patients with diseases of the nervous system other than multiple sclerosis. Therefore the present study was undertaken to extend observations on the effect of hyperthermia on patients with multiple sclerosis and to study the effect of hyperthermia on patients with a variety of other neurological diseases.

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Methods and Materials

A series of 100 subjects were studied: 16 intact subjects; 12 subjects with multiple sclerosis, and 72 patients with a variety of other neurological diseases. The normal group included 15 young men and 1 young woman. Before immersion in hot water, vital signs, visual acuity, grip strength, deep tendon reflexes, plantar responses, pupillary size, dysarthria, nystagmus, range of extraocular movements, and mental state were recorded. The subjects were then immersed in a bathtub up to the nipple line in water at 104 F. During the next 5 minutes the water temperature was raised to 110 F, and they remained in the water for 20 to 30 minutes. During this period repeated examinations were carried out. After the water was drained, the subjects, still reclining in the tub, were examined at intervals until control levels were reached.

A spring dynamometer was used to test grip. A Lebensohn [4] near-vision chart was used to test visual acuity, and acuity was tested uncorrected. (The collection of water vapor and perspiration on the lenses of glasses and the occurrence of nystagmus made refraction unreliable.)

Results of Immersion of Normal Subjects

Three of the sixteen intact subjects developed objective neurological changes (Table 1). Vital-sign changes were approx-

TABLE 1.—*Neurological Changes (Except Mental) Observed During Hot Water Immersion*

Groups	No Neurologic Changes Observed	Neurologic Changes Observed	Type Change	
Normal, 16	13	3	Tetany	2
			Grip decrease *	1
Normal, 3 (after IV phenobarbital)	1	2	Nystagmus	2
Patients with various neurological diseases, 84	32	52	Visual acuity decrease †	7
			Reflex ‡	10
			Hyporeflexia	4
			Hyperreflexia	6
			Grip	18
			Decrease	12
			Increase	6
			Plantar reflex	4
			Flexor to abnormal	2
			Extensor to normal	2
			Nystagmus	33
			Seizures	3
			Visual field	4
			Medial longitudinal Fasciculus syndrome	9
			Miscellaneous	
			Ptosis	3
			Facial and E.O.M. palsy	3
			Anisocoria	1

* Greater than 25% change.
† Greater than a 2-line change on near-vision chart.
‡ Greater than 2+ change.

imately equal in normal and in patient groups, as shown in Table 2. The diastolic blood pressure fell in all cases; the systolic pressure usually fell but occasionally rose. The neurological changes occurring in the three intact subjects were tetany, in two, and a decrease in grip strength, in one. Grip strength was considered changed only if it increased or decreased 25% from control levels. Tetany was manifested by tingling of the face, scalp, and extremities; carpopedal spasm; hyperactive reflexes, and a positive Chvostek sign.

Comment.—Other subjects occasionally complained of nausea, headache, tingling of the arms and legs, and epigastric discomfort. These symptoms occurred with about the same frequency in the patients and in intact subjects. Less often observed were mental symptoms of irritability, restlessness, agitation, lethargy, and euphoria.

Results of Immersion of Patients with Neurological Diseases

Eighty-four patients, with 24 different diseases, were tested. Diagnostic categories studied are listed in Table 3. Thirty-two of these showed no neurological changes during immersion in hot water except mental ones (Table 1). Fifty-two of the patients did show neurological changes. They are described below under the following headings: (*a*) oculomotor, (*b*) visual, (*c*) reflex, (*d*) strength, and (*e*) seizures.

A. Oculomotor Changes.—Nystagmus was estimated on right and left lateral gaze and on vertical gaze. The nystagmus was graded 1+ to 4+ on the basis of the amplitude of the oscillation, 1+ being fine motion of low amplitude and 4+ being gross movement of high amplitude. Nystagmus was considered significant only if persistent and if a change of two steps was achieved. Thirty-three patients developed nystagmus or showed an increase in preexisting nystagmus.

Sixteen of these developed nystagmus during immersion who did not have it on control observation. Seven of these patients developed both horizontal and vertical nystagmus, and nine patients developed horizontal nystagmus alone.

Seventeen showed an exaggeration of preexisting nystagmus or developed nystagmus in additional directions of gaze. Five of these developed vertical nystagmus who had only horizontal nystagmus. Three showed an increase in horizontal nystagmus alone. Nine patients showed an increase in previously existing horizontal and vertical nystagmus.

In this group of 33 patients, there were 9 patients with multiple sclerosis, 12 with

TABLE 2.—*Vital Sign Changes of Normals and Patients*

Group Studied	Sex		Mean Age	Mean Maximal Temperature (F)	Mean Systolic Fall and S.D.*	Mean Diastolic Fall and S.D.*
	Males	Females				
Normals	15	1	27.5	102.9±0.7	11±19	51±20
Patients without neurological change	28	4	46.0	101.7±0.3	14±23	43±25
Patients with neurological change	42	10	42.8	101.8±1.2	16±21	43±20
Patients with multiple sclerosis	8	4	41.3	101.5±1.5	17±15	43±23

* Standard deviation.

TABLE 3.—*Diagnostic Categories With and Without Neurological Changes* *

Diagnosis	Changes Observed	No Changes Observed	Total
Normal	3	13	16
Spine fracture, old		1	1
Seizures, focal and other	7	1	8
Idiopathic	7	4	11
Post-traumatic	4	1	5
Encephalopathy			
Vascular	2	5	7
Post-traumatic	4	4	8
Wernicke's	1		1
Post-infectious		1	1
Diabetic neuropathy		1	1
Peripheral nerve injury		1	1
Peripheral neuropathy, nutritional		3	3
CNS syphilis	3	3	6
Herniated nucleus pulposus			
Lumbar	1	4	5
Labyrinthitis	1	1	2
Cerebellar degeneration			
Alcoholic-nutritional	1	2	3
Myotonia atrophica		1	1
Charcot-Marie-Tooth syndrome		1	1
Guillain-Barré syndrome		1	1
Thoracic outlet syndrome	1		1
Subacute combined degeneration	1		1
Basilar artery insufficiency	1		1
Friedreich's ataxia	1		1
Brain metastases, multiple	1		1
Pituitary tumor	1		1
Heredofamilial CNS disease	1		1
Old poliomyelitis	1		1
Cauda equina compression	1		1
CNS disease of ? etiology	5		5
Multiple sclerosis	12		12
Total			108

* One hundred (100) patients studied, with total of 108 major diagnostic categories.

seizure disorder, 10 with diffuse diseases of the central nervous system, 1 with labyrinthitis, and 1 with cauda equina compression.

Of the 12 patients with seizure disorders, 7 were receiving diphenylhydantoin (Dilantin) and phenobarbital at the time of immersion. To investigate the possible role played by the oral barbiturates in inducing nystagmus, two normal subjects who had not shown nystagmus while immersed received 60 and 130 mg., respectively, of phenobarbital I. V. No nystagmus was seen until they were immersed; one developed nystagmus in the horizontal plane; the other, both in the vertical and in the horizontal plane.

Of the 12 patients with multiple sclerosis, 9 developed eye movement changes which were interpreted as representing the syndrome of dysfunction of the medial longitudinal fasciculus. These changes were paralysis of the adducting eye on lateral gaze, the preservation of the ability to converge, and a predominance of nystagmus in the abducting eye (dissociated nystagmus).* Six of the nine patients with multiple sclerosis showed bilateral paralysis of the adducting eye on lateral gaze; two showed it on right lateral gaze, and one on left lateral gaze. Four patients showed poor convergence during the immersion, probably due to inattention and mental changes; but there was more contraction of the medial rectus muscles on convergence attempts than on lateral gaze.

On control examination, three patients showed dissociated nystagmus (predominance of nystagmus in the abducting eye). Similar dissociated nystagmus appeared in three additional patients after immersion and prior to the development of paralysis of the adducting eye. Six patients, therefore, showed more nystagmus in the abducting eye prior to the onset of the other components of the syndrome of dysfunction of the medial longitudinal fasciculus.

There were three instances of ptosis—two of isolated extraocular muscle palsies and one of anisocoria. All these signs occurred in patients with multiple sclerosis.

B. Visual Function.—Seven patients showed a significant decrease in visual acuity in one or both eyes. At least a two-line change on the near-vision chart was necessary to be significant. Five of these patients had a diagnosis of multiple sclerosis.

The appearance of nystagmus on direct forward gaze rendered patients with multiple sclerosis unsuitable for visual field testing. Gross visual field change during immersion were seen in four patients with disorders other than multiple sclerosis. These disorders were insufficiency of posterior cerebral arteries, central nervous system disease of unknown etiology, intrasellar and suprasellar tumor, and Friedreich's ataxia. In the first three cases an attempt was made to reproduce the field defects with the feet and legs immersed to the midcalf in water at 110 to 115 F for 20 minutes before

* This syndrome was first described by Spiller [8] and experimentally produced by Bender and Weinstein.[6,7]

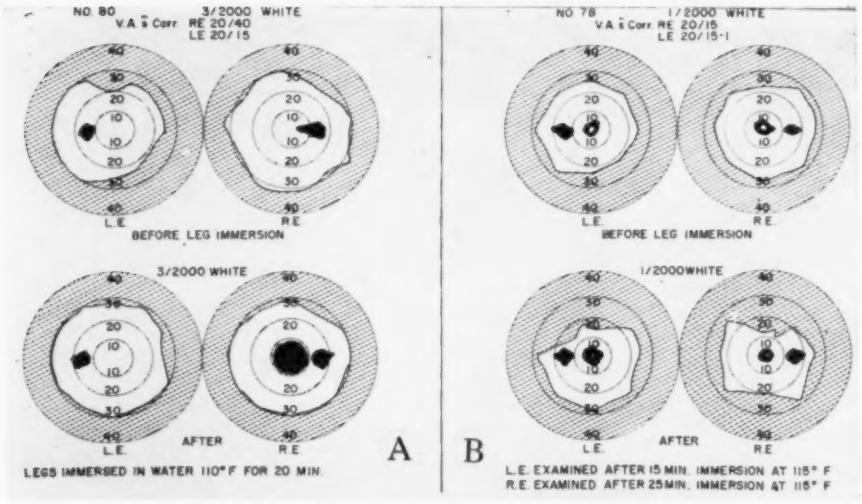

Fig. 1.—Visual field changes in two patients with neurological disease on immersion of the legs in hot water at 110 to 115 F.

repeating the field determinations. Two of these patients showed visual field changes under this test situation. Figure 1*A* shows the appearance of a central scotoma in the right field of vision in the patient with the central nervous system disease of unknown etiology. Figure 1*B* shows the development of a superior altitudinal field defect in the patient with insufficiency of the posterior cerebral arteries.

C. Reflex Changes.—Four patients showed a change in the plantar reflex; in two it became abnormal, and in two it reverted to normal (Table 4). These changes reversed to control levels in from 2 to 7 minutes in three patients, and in one (Friedreich's ataxia) the plantar reflex remained flexor for 12 hours before again becoming extensor.

Deep tendon reflexes were graded 0 to 4+, and a 2+-step change in this gradation was considered significant. Ten patients with various neurological diseases showed alterations in deep tendon reflexes. In each instance the ankle jerks were the only reflexes which changed. Six showed an increase, and four showed a decrease. These reflexes returned to normal in from 2 to 10 minutes. No patient with multiple sclerosis showed altered deep tendon reflexes.

TABLE 4.—*Plantar Reflex Changes*

Patient No.	Age, Yr.	Diagnosis	Type Change
A	38	Multiple sclerosis	Extensor to flexor bilaterally
B	34	Friedreich's ataxia	Extensor to flexor bilaterally
C	39	Cauda equina compression	Flexor to abnormal bilaterally
D	52	Cervical cord compression	Flexor to abnormal right

D. Change in Power.—Subjective complaints of weakness were frequent, and many patients appeared to have generalized weakness. An attempt was made to measure objectively grip-strength changes using the spring dynamometer. This instrument was found to be useful only in patients who had no profound weakness. A 25% change from control levels was considered significant. Sixteen patients with various neurological diseases and two normal subjects showed a significant change. Eleven showed a decrease in grip strength; two showed an increase, and one showed an increase in one hand and a decrease in the other. No one diagnostic category showed this change consistently. A decrease in grip strength was observed in only one patient with multiple sclerosis, in contrast to the findings of

TABLE 5.—*Changes Shown by Patients with Multiple Sclerosis*

Patient No.	Sex and Age, Yr.	Neurological Changes	Mental Changes	Other Changes
1	M 32	Bilateral MLF syndrome; decreased visual acuity, right eye	Agitation; sleeping	Pale, cold, clammy, retching
2	F 39	Increased nystagmus; left MLF syndrome; decreased visual acuity bilaterally	Sleepy	--
3	M 38	Bilateral MLF syndrome; extensor plantars to flexor plantars	--	Diplopia; generalized weakness
4	M 46	Increased nystagmus; bilateral MLF syndrome; superior rectus weakness, left eye	Agitation	Generalized weakness
5	M 50	Increased nystagmus; bilateral MLF syndrome; ptosis, right eye; dysarthria	Agitation	--
6	F 33	Increased nystagmus; right MLF syndrome; bilateral ptosis; divergent strabismus; right facial palsy; decreased visual acuity bilaterally	Agitation; sleeping; unresponsive	--
7	M 55	Horizontal and vertical nystagmus; bilateral MLF syndrome; bilateral ptosis; decreased visual acuity bilaterally	Sleeping; unresponsive	Forced laughing
8	M 36	Horizontal and vertical nystagmus; right MLF syndrome; weakness of left medial rectus muscle; decreased visual acuity bilaterally	Sleeping	--
9	M 43	Increased nystagmus; bilateral MLF syndrome; oscillopsia; spontaneous ankle clonus; more ataxia of legs	--	--
10	M 52	Increased horizontal nystagmus	--	--
11	F 24	Increased horizontal nystagmus	Agitation; angry	--
12	F 48	60% decrease in grip, left	--	--

Guthrie,[2] who reported a consistent decrease in grip strength in patients with this disease.

E. Occurrence of Seizures.—Of the 24 patients tested who had seizure disorders, 3 developed seizures in the hot bath.

Neurological Changes in Patients with Multiple Sclerosis

All of the patients with multiple sclerosis showed neurological changes, as shown in Table 5. These included ocular evidence of the syndrome of dysfunction of the medial longitudinal fasciculus, changes in the plantar responses, decrease in visual acuity, ptosis, facial and extraocular muscle palsies, nystagmus, dysarthria, anisocoria, and mental changes. Changes averaged 2.8 per patient in the multiple sclerosis group, as compared with 0.8 change per patient in those with other diseases.

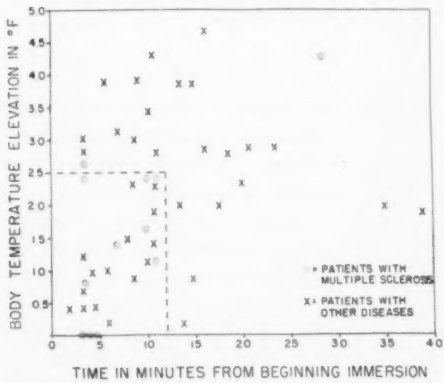

Fig. 2.—Time and temperature relationship of the first neurological sign.

The tendency for first changes to occur earlier and at lower elevations of body temperature in patients with multiple sclerosis is shown in Figure 2. At 12 minutes of immersion, 11 out of 12 of the multiple sclerosis group had shown the first change, as compared with 24 out of 38 of those with other diseases. When the body temperature had been raised 2.5 F, 10 out of 12 of the patients with multiple sclerosis had shown a first change, in comparison with 22 out of 38 in the other group. When time and temperature are considered together, 10 out of 12 patients with multiple sclerosis had shown a first change before 12 minutes of immersion and prior to elevation of body temperature by 2.5 F. This is in contrast to 15 of 38 of those with other diseases. (The patients just discussed are those with

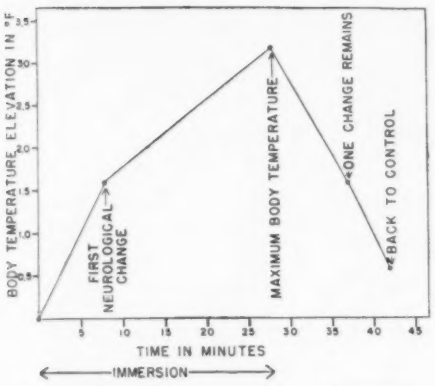

Fig. 3.—Temperature at the time of appearance and disappearance of signs.

values plotted within the dotted line in Figure 2.)

The type of first changes observed differed in the two groups. Patients with multiple sclerosis often showed changes in the extraocular movements, excluding nystagmus. This was never observed in other neurological diseases. In the group of other neurological diseases, the deep tendon reflexes were observed to change first in eight instances and the plantar reflexes first in three instances. These changes did not occur in patients with multiple sclerosis.

The first changes generally were observed as the oral temperature began to rise (Fig. 3). The values recorded are the average for the 12 patients with multiple sclerosis. The first changes appeared after eight minutes of exposure, when the oral temperature had been elevated 1.6 degrees (F). As the temperature reached its maximum, the patients developed other neurological signs. As the oral temperature fell, the signs began to disappear until, at 37 minutes, when the temperature was elevated 1.7 degrees (F) above normal, only one change remained. All signs had disappeared as the average body temperature elevation fell 0.6 degree (F) at 42 minutes. It is interesting that the temperature at which the first sign appeared and the temperature at which only one sign remained are about the same. In general, there appeared to be a relationship between the appearance and disappearance of signs and the rise and fall in body temperature. Within five minutes of immersion three patients with multiple sclerosis showed the onset of neurological change, and at this point an elevation of oral temperature had not yet been recorded.

The patients who had minimal to moderately advanced multiple sclerosis showed fewer changes (Patients 10 and 12, Table 5) than the other 10 patients, who had more advanced disease. Two of the latter became unresponsive while in the bath, and they returned to control levels in from four to seven minutes after the immersion was discontinued.

Three patients who had shown the syndrome of dysfunction of the medial longitudinal fasciculus when immersed to the nipple line were tested with only the legs immersed to the level of the knees in water of 115 F. They developed the first neurological sign when the oral temperatures were elevated 0.4 to 1.4 degrees (F). One patient (No. 5) developed a medial longitudinal fasciculus syndrome after 14 minutes of leg immersion. The other two patients did not develop the medial longitudinal fasciculus syndrome. One patient (No. 4) developed palsy of right lateral gaze and dissociated nystagmus on left lateral gaze. The other patient (No. 6) developed bilateral ptosis and had a very weak voice. She yawned frequently and slept intermittently during the examination.

Comment

It has been shown that patients with multiple sclerosis developed earlier and more frequent neurological changes, and at lower elevations of body temperature, than did the patients with other neurological diseases. There also seemed to be a relationship between body temperature elevation and the appearance and disappearance of signs. That is to say, when the body temperature was elevated above normal, the changes appeared; and when it was lowered, they disappeared. Changes in the mental state, eye

movements (including nystagmus), and visual acuity were alterations the most frequently observed.

Forty other patients, with 19 different neurological diseases other than multiple sclerosis, also developed neurological changes which were considered significant. These included changes in reflexes, new or increased nystagmus, seizures, changes in plantar responses, increase or decrease in deep tendon reflexes, decrease in strength, decrease in visual acuity, and mental changes. Daily fluctuations are sometimes seen in the neurological examination in patients with neurological diseases. This study suggests that, among other things, changes in body temperature may play a part in the production of these changes. The frequency with which agitation, irritability, and anger were observed suggests that these mental symptoms were similar to those seen with delirium during fever.

Nystagmus appeared or was increased in a wide variety of neurological diseases. Quantitation of nystagmus does not lend itself to standardization and may vary with the observer; therefore, the nystagmus which developed in 16 patients who did not have it prior to immersion is a more significant finding than that nystagmus which was observed to increase. While this study was in progress, we began to examine carefully patients with neurological diseases for nystagmus during febrile episodes, and we have occasionally observed the appearance and disappearance of nystagmus in these patients. From these observations it appears that nystagmus which comes on during fever in a patient with neurological disease may be a transitory finding, provoked by body temperature elevation. It is doubtful that the nystagmus which appeared during elevation of the body temperature was a caloric response, as no nystagmus was seen in the normal subjects under the same test situation until after an intravenous barbiturate was given. The administration of oral barbiturates does not consistently predispose to the development of nystagmus, for five patients who were receiving oral diphenylhydentoin and phenobarbital at the time of immersion showed no nystagmus during immersion.

The nine patients who during immersion in hot water developed all the components of the syndrome of dysfunction of the medial longitudinal fasciculus had moderately to far-advanced disease of the nervous system. All of them by history or physical examination gave evidence of dysfunction of ocular motility, and the following signs and symptoms were present singly or in combination prior to the immersion: a history of diplopia, weakness of one or more extraocular muscles, dissociated nystagmus, and vertical nystagmus. Owing to these findings, it is assumed that there was preexisting damage to the medial longitudinal fasciculus and all components of the medial longitudinal fasciculus syndrome appeared after these nine patients were immersed in the hot bath. In six of these, dissociated nystagmus was present prior to the development of other components of the medial longitudinal fasciculus syndrome. It may be that the presence of more marked nystagmus in the abducting eye indicates early damage to this fasciculus.

One patient with multiple sclerosis, not in our study group, as observed by us during an acute febrile episode. During this period, the patient had a unilateral medial longitudinal fasciculus syndrome. It cleared on defervescence. Recently, Coddon [8] reported the appearance and disappearance of a medial longitudinal fasciculus syndrome during typhoid therapy in a patient with multiple sclerosis.

In two patients, visual field changes were demonstrated by immersing the feet and legs alone, a technique used by Guthrie [2] on patients with multiple sclerosis. This technique may be of value in bringing out latent field defects in patients with various types of neurological diseases. It seemed that the nystagmus which developed upon feet-and-leg immersion was not as intense as that which developed during partial-body

immersion; therefore, the fixation interference due to nystagmus may be lessened during feet-and-leg immersion.

Visual acuity was rather low on control observations in the group which showed changes, perhaps due to the advanced age of the patients, the neurological diseases studied, and the fact that vision was tested uncorrected and that the patients had to accommodate while reading the near-vision chart. Though accommodation difficulty may have added to visual loss in these patients, the decrease in visual acuity confirms that finding by Guthrie [2] and by Edmund and Fog.[3]

The occurrence of convulsions in patients who have seizure disorders in hot baths has been reported by Hopkins [9] and by Mehrtens and Allred.[10] Fifteen per cent of Hopkins' patients had convulsions after 20 to 45 minutes of immersion in hot water. There was respiratory alkalosis, a drop in ionized blood calcium, blood dilution, and a drop in blood sugar. The above factors were listed as contributing to the convulsions, as well as hyperventilation.

Two normal subjects of the present study developed tetany in the hot bath. They both had hyperpnea. Rosett [11] described the sequence of symptoms in normal subjects who hyperventilated until tetany appeared, and this was the sequence we observed. We assume that hyperventilation with respiratory alkalosis led to tetany in these two subjects. The tingling of the extremities and the hyperreflexia seen in some patients in this study may have been early signs of tetany.

The mechanism of the neurological signs and symptoms during induced hyperthermia has not been explained. Whether or not changes occur prior to measurable elevations of body temperature is not clear and merits further study. Guthrie [2] showed that an arterial tourniquet applied to the immersed extremity would prevent changes in neurological signs from occurring. Gibbon and Landis [12] have shown that when one extremity is immersed in warm water, the skin temperature elsewhere rises, and this, too, can be prevented by the use of an arterial tourniquet. This phenomenon may be due to the stimulation of the hypothalamus by warmed blood, with a resulting autonomic discharge and vasodilatation in the extremities.

It is possible that when the body is immersed in hot water, there is some local humoral response, and some substance is released into the circulation which causes neurological changes by its influence upon the central nervous system. It is also possible that heat itself can cause these changes by its direct effect upon the central nervous system. This study suggests that heat alone may be responsible for the observed neurological changes.

Summary and Conclusions

A series of 100 subjects, 16 normal persons and 84 patients with neurological diseases, were immersed in water at 104 to 110 F. and observed for neurological changes.

There were 2 instances of tetany, manifested by carpopedal spasm, hyperactive reflexes, and a positive Chvostek sign, and 1 instance of decreased grip strength in the 16 normal subjects who were immersed.

Each of the 12 patients who had multiple sclerosis developed neurological changes, which occurred more frequently and, in general, at a lower elevation of body temperature than in patients with other diseases of the nervous system.

The appearance and disappearance of neurological signs often paralleled the rise and fall of body temperature in patients with multiple sclerosis, but changes occasionally occurred without any elevation in body temperature.

Because patients with multiple sclerosis can develop serious neurological dysfunction on exposure to heat, they should avoid excessive heat, especially hot baths.

Of a group of 72 patients with diseases of the nervous system other than multiple sclerosis, 40 showed significant neurological changes. These were the development of or

intensification of nystagmus, in 24 patients; appearance of visual field changes, in 4 patients; change in the ankle jerk, in 10 patients; decrease in grip strength, in 10 patients; appearance of seizures, in 3 patients; change in the plantar response, in 3 patients, and decrease in visual acuity, in 2 patients.

Mental changes were observed in both the intact and the patient groups, but more frequently in the latter, and especially so in patients with multiple sclerosis.

Nine of twelve patients with multiple sclerosis developed the syndrome of dysfunction of the medial longitudinal fasciculus. Six of these had predominance of nystagmus in the abducting eye prior to the appearance of other parts of the syndrome. Such changes were not seen in the 72 patients with other diseases of the nervous system.

Nine patients with multiple sclerosis developed nystagmus or showed an intensification of preexisting nystagmus; five showed a decrease in visual acuity; one showed a decrease in grip strength, and one developed a change in the plantar response. Such changes were also seen in 40 of a group of 72 patients with other diseases of the nervous system.

The Multiple Sclerosis and Demyelinating Disease Clinic, Hospital for Special Surgery, cooperated in this study.

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Meningeal Hemangiopericytoma

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In 1942 Stout and Murray[1] described a group of vascular neoplasms which they suggested were derived from the capillary pericytes of Zimmermann,[2] and classified these tumors as hemangiopericytomas. The histologic appearance of the hemangiopericytoma was distinct from that of the hemangioma, hemangioendothelioma, or glomus tumor, and its identification was facilitated by the use of silver impregnation techniques for the demonstration of reticulum.

The hemangiopericytoma is not rare, despite the relative paucity of recorded examples of such tumors. Reports have indicated that they are found with equal frequency in both sexes and in all age groups. Approximately one-third of the cases have demonstrated malignant characteristics, as evidenced by distant metastases or local invasion and recurrence.[3] Such neoplasms have been observed in a wide variety of locations, as might be expected from the ubiquitous distribution of blood vessels throughout the body. Although perhaps most frequent in the soft tissues, authenticated examples have been described in such locations as the uterus,[4] orbit,[5] sigmoid colon,[6] retroperitoneal[6] and omental tissues.[7] Recently Begg and Garret[8] reported a case of such a lesion arising in the meninges. These authors suggested that this was the first example of such a neoplasm, although they indicated that similar tumors were depicted as angioblastic meningiomas by Bailey, Cushing, and Eisenhardt in their classical essays on meningiomas.[9,10]

Recently we have encountered an instance of a recurrent, fatal meningeal neoplasm which histologically fulfills the diagnostic criteria of hemangiopericytoma. Certain unusual morphologic features of this neoplasm and the clinical course exhibited by the patient merit this report.

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Report of a Case

A 24-year-old, right-handed man began having intermittent headaches on the left, pain in the left ear, and discomfort in the erect position in February, 1954, while he was a paratrooper in the Army. This onset was followed by weight loss and difficulty in reading and in naming objects. After hospitalization he developed papilledema and became comatose. Ventriculography revealed a left temporal lobe lesion. A left temporal craniotomy was performed on Aug. 24, 1954, and a large tumor was found invading the dura, the squamous portion of the temporal bone, and the floor of the left middle fossa, extending upward over the temporal lobe. He received 4500 cc. of blood during the operation, and the procedure was terminated with incomplete removal of the neoplasm because of the vascular operative field. One month later the remainder of the tumor was removed from the left petrous ridge, and in its removal the mastoid cells were entered. Three months later a tantalum cranioplasty was performed, and the patient was discharged from the hospital with no neurological deficits.

During April, 1955, the patient again experienced headache and difficulty in reading. Arteriography revealed a "tumor stain" just superior to the left petrous ridge. Exploration of this area revealed a very vascular extracerebral neoplasm, which weighed 100 gm. This tumor was firmly attached along the left petrous ridge and neighboring portions of the temporal squama and floor of the temporal fossa, and was sharply separated from the surrounding brain. Hypotension induced with trimethaphan camphorsulfonate (Arfonad) reduced the severe hemorrhage which occurred during the initial phases of the operation. Following operation he was given a total skin dose of 5900 r to the left frontotemporoparietal area over a one-month period, or a tumor dose of approximately 4200 r to a point 5 cm. in depth.

Three months before his admission to the Veterans' Administration Hospital, Pittsburgh, he began having headache on the left side, blurred vision, and difficulty with speech, reading, and writing. Examination revealed a horseshoe-shaped scar in the left temporal area. The skin over a palpable cranial defect was moderately tense. Alopecia and pigmentation were present over the left side of the head. Minimal expressive aphasia was present. Auditory acuity was decreased on the left.

Radiographic study of the skull demonstrated a large bony defect in the left temporoparietal region, the upper half of which was covered with a metallic plate. Left angiography showed upward displacement of the left middle cerebral artery.

A left temporofrontal craniotomy was carried out under medium-deep hypothermia on Aug. 15, 1956. While the patient was under intratracheal nitrous oxide-ether anesthesia, his body temperature was reduced by circulating cooled alcohol in the coils of a body mattress. A left sagittal scalp flap was used to expose the previous operative area. The dura was opened when the patient's body temperature was 29.3 C (84.7 F) rectally. A large, firm extracerebral neoplasm was removed in fragments from the floor of the middle cranial fossa, petrous ridge, and sphenoid wing. A dural attachment and area of bony invasion of the tumor on the floor of the middle fossa posterior to the sphenoid wing were removed with a curette and the area coagulated. The remainder of the floor of the middle fossa appeared to be covered with a glistening membrane. After removal of the tumor the patient's temperature was returned to normal levels in five hours by circulating warm alcohol through the coils of the mattress. Blood loss was minimal during the operative procedure.

Twelve days following operation the patient developed headache, stiff neck, and drainage of cerebrospinal fluid from the left ear. Exploration of the wound revealed a dural defect 5 cm. in diameter in the area of the glistening membrane on the floor of the middle fossa. This dural de-

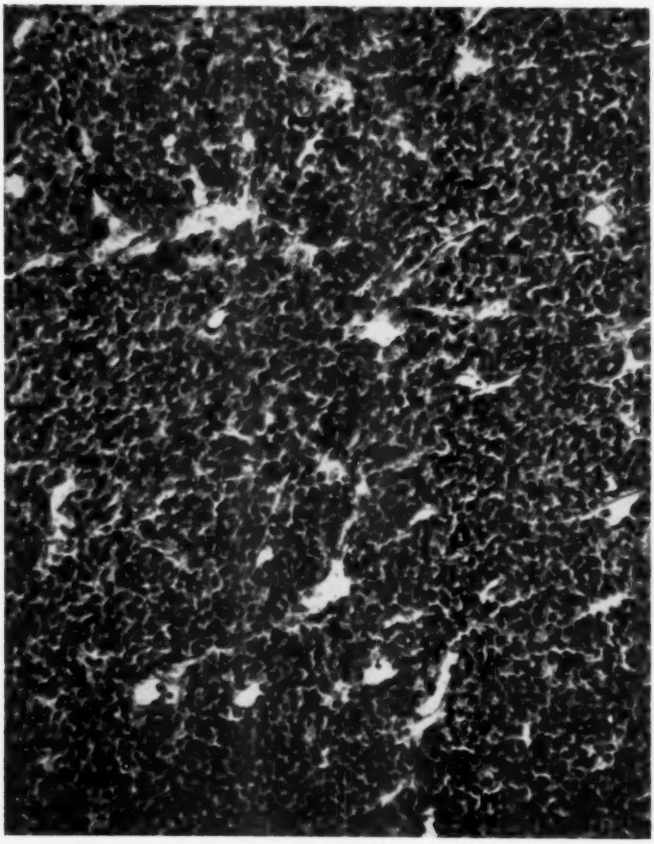

Fig. 1.—Photomicrograph of hemangiopericytoma revealing distinct endothelial-lined spaces surrounded by relatively undifferentiated round and ovoid tumor cells. × 200.

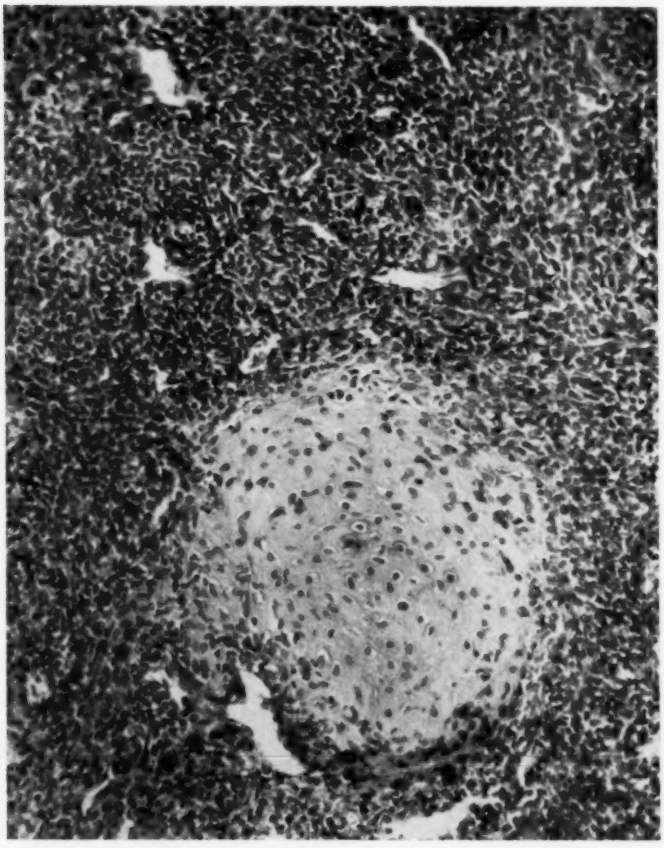

Fig. 2.—Area from the hemangiopericytoma revealing a perivascular pattern similar to that noted in Figure 1. A focus of osteoid is also apparent within the substance of the neoplasm. × 175.

fect involved the entire petrous ridge and the floor of the middle fossa. Two bony defects in the petrous ridge were packed with bone wax, and a periosteal graft was sutured into the dural defect.

Cultures of the cerebrospinal fluid revealed Aerobacter aerogenes, which was sensitive to chloramphenicol U. S. P. (Chloromycetin) in vitro. This substance was administered intramuscularly in 500 mg. doses every six hours. Eight days after operation purulent drainage occurred from two openings in the old scalp incision in the area of scarring from previous irradiation. The patient's course was characterized by increasing confusion, aphasia, and persistent nuchal rigidity. During packing of the wound on Sept. 17 massive hemorrhage occurred; he became comatose and died the next day.

Microscopic Description of Neoplasm.—Sections of tissue fixed in Zenker's acetic acid fluid and stained with hematoxylin, eosin, and methylene blue revealed a neoplasm formed by aggregates of round to spindle cells of moderate size with slight, pale-staining cytoplasm and vesicular, round and ovoid nuclei (Fig. 1). The nuclei were uniform but moderately hyperchromatic. Mitoses were frequent, but atypical forms were not evident. Scattered throughout the cell aggregates were endothelial-lined spaces of varying sizes, some of which contained red blood cells. The endothelium of these spaces was uniform and flat. In some areas the tumor cells appeared to be radiating about these vessels, although a distinct organoid pattern was not apparent. In rare foci within the substance of the tumor, its cells merged with small zones of osteoid and apparently immature cartilage (Fig. 2), as evidenced by their appearance when stained with the Van Gieson technique; the osteoid appearing pink and the cartilage light-yellow or unstained. In addition, some zones interpreted as representing osteoid contained minimal deposits of calcium and the early formation of cement lines. Connective tissue septa of varying thickness were observed coursing throughout the neoplasm, but

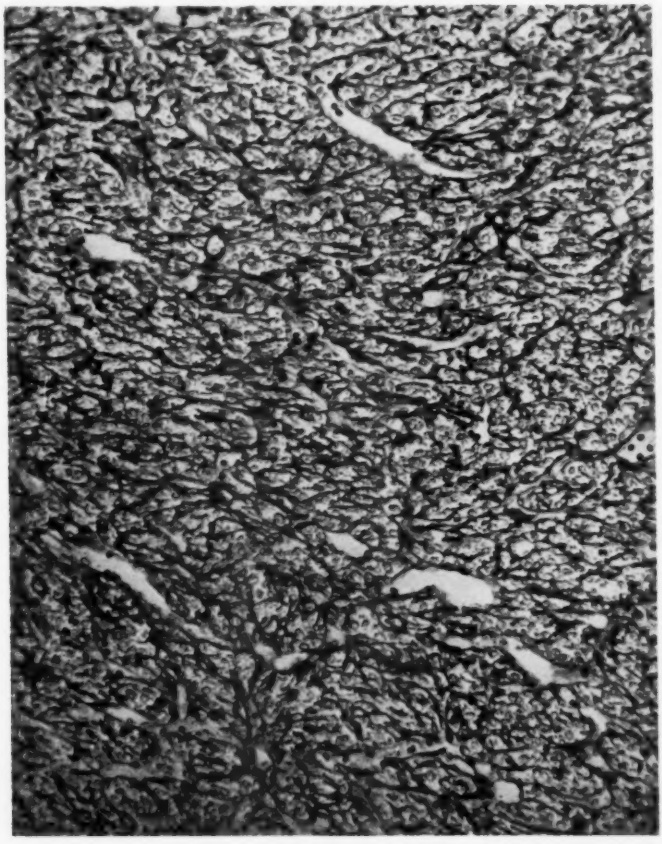

Fig. 3.—Reticulum stain of hemangiopericytoma of the meninges revealing characteristic pattern of fibers about groups and individual tumor cells. The vascular spaces are clearly outlined. × 185.

definite encapsulation was not encountered and infiltration of bone was observed. Sections stained by the Wilder reticulum method clearly outlined vascular walls and illustrated the extraluminal location of tumor cells (Fig. 3). Delicate strands of reticulum were apparent about groups of cells, as well as individual cells. Sections stained by the phosphotungstic-acid hematoxylin, oil red O, and periodic acid-Schiff techniques failed to reveal cellular fibrils, intracellular lipid, or glycogen.

Review of sections prepared from previous operative specimens revealed an identical morphologic appearance of the neoplasm.

Necropsy Findings.—Significant findings were limited to the brain.

Gross Examination of Brain: The convolutions were flat and the sulci shallow. A large defect, measuring 8×8 cm., in the temporoparietal area representing the operative site, was covered by dense white tissue (periosteal graft). The meninges at the base of the brain were opaque. A slight cerebellar pressure cone was apparent. The cut surface of the brain revealed marked dilation of the lateral ventricles, which contained old and recent hemorrhage. A zone of hemorrhage and necrosis communicated between the operative defect and the left lateral ventricle. The aqueduct was also dilated, and the fourth ventricle was occluded by a recent blood clot.

Microscopic Examination: Numerous microscopic sections prepared from the operative site failed to reveal neoplasm. Moderate cerebral edema was evident. A purulent exudate was present within the meninges of the cerebellum and was also noted within the perivascular spaces. The periosteal graft also revealed granulation tissue, foreign-body reaction, and foci of polymorphonuclear cells, lymphocytes, and plasma cells. Moderate satellitosis and degranulation of ganglion cells were observed in areas of hemorrhage noted about the lateral and fourth ventricles.

Comment

Except for the rare foci of immature cartilage and osteoid, the morphologic features of this meningeal neoplasm are typical of hemangiopericytoma. Demonstration of the distribution of reticulum within this tumor by silver impregnation allows its differentiation from other cellular tumors derived from blood vessels, such as the glomus tumor and the hemangioendothelioma. Unlike the latter, the reticulum stain clearly reveals the extraluminal position of the tumor cells, and, although the presence of reticulum is noted about the individual cells, this is not as pronounced or as consistent as in glomus tumors. Further, the reticulum pattern observed in this neoplasm and in other cases of hemangiopericytoma differs from that encountered in several examples of the more familiar meningiomas which we have had the opportunity to examine with the silver technique. The lack of intracellular lipid, glycogen, or fibroglial or myoglial fibers in this tumor has been noted previously by one of us (E. R. F.) in a hemangiopericytoma located in the soft tissues of the thigh.[11]

The presence of rare foci of osteoid and immature cartilage within the main substance of this neoplasm raises the question whether this lesion might not be classified as an osteoblastic or a chondroblastic meningioma. Unfortunately, accounts of the latter are infrequent, and often insufficiently documented to permit accurate comparisons. It is noteworthy, however, that the osteoblastic meningiomas described by Cushing and Eisenhardt,[10] although possessing osseous foci, were also comprised of cellular elements identical with those of the psammomatous type of meningioma and clinically were considered as slow-growing tumors. The morphologic features and reticulum pattern of the more familiar psammomatous type of meningioma were not observed in the present tumor, and the rapidity of its growth was illustrated by the clinical course exhibited by this patient. The one example of chondroblastic meningioma depicted by these authors was considered by them to represent chondrosarcoma. Undifferentiated mesenchymal cells comprised a large portion of the neoplasm. It is interesting to note that the reticulum pattern illustrated is, in areas, not unlike that revealed in the present tumor, as well as in other hemangiopericytomas, and a prominence of vessels was noted by these authors. Similarly, the reticulum pattern and cellular detail of the meningiomas classified as angioblastic by Cushing and Eisenhardt,[10] and previously by Bailey, Cushing, and Eisenhardt,[9] are identical with those of this tumor and other hemangiopericytomas. This similarity prompted Begg and Garret,[8] in their report of a case of meningeal hemangiopericytoma, to consider the angioblastic meningiomas as actually representing hemangiopericytomas. We concur with their conclusions and also consider the foci of osteoid and immature cartilage in this lesion to represent foci of metaplasia or developmental variation in growth potential exhibited by these neoplastic cells, although such foci, to our knowledge, have not heretofore been described in hemangiopericytomas elsewhere. Tissue culture studies of these latter have offered evidence that the capillary pericyte represents the cell of origin of this neoplasm.[11,12] That such cells possess multiple developmental potentials is apparent from the frequent morphologic variations noted in sections of these tumors and their growth in tissue culture. A similar phenomenon is well recognized in other primitive mesenchymal neoplasms in which foci of various mesenchymal elements may be encountered. It is of interest in this regard that Bailey, Cushing, and Eisenhardt[9] proposed a similar explanation to account for the various types of meningioma, indicating that the cellular components are capable of differentiating into fibroblastic, angioblastic, osteoblastic, and "other types of cells."

The clinical behavior of the neoplasm in this instance was also in keeping with the diagnosis of hemangiopericytoma. Although in the other case of such a tumor in

the meninges, described by Begg and Garret,[8] the neoplasm did not infiltrate the bone or tend to recur, such an event was not unusual with the so-called "angioblastic meningiomas" of Cushing and Eisenhardt [10] or with hemangiopericytomas in other locations. Although it has been stated that the behavior of such neoplasms cannot be determined by histologic study, certainly the presence of mitoses in such tumors, as indicated previously,[11] might be considered an ominous finding in a hemangiopericytoma.

The case indicated that surgical excision is the treatment of choice for meningeal hemangiopericytoma. The employment of hypothermia in the operative procedure was thought to be responsible for making the operative procedure technically easier by reducing the marked blood loss encountered in the previous operations. Despite the large size of the recurrence on each occasion, surgical removal resulted in minimal neurological deficit. In view of the rapid recurrence of the tumor, it was apparent that irradiation had little effect in impeding such growth. Comparison of pre- and post-irradiation tumor specimens revealed no recognizable differences. Irradiation necessitated a very large skin flap in the fourth operative excision and made surgical removal of the recurrent neoplasm more difficult. The breakdown of the old skin incision and the poor healing in the irradiated areas of the skin flap were undoubtedly important contributing factors in the final outcome in this case.

The spinal fluid otorrhea was of interest, since it was not recognized that spinal fluid communication had been made between the external ear and the dural defect in removal of the neoplasm in the bony petrous ridge. This fistula was corrected by the periosteal graft over the floor of the middle fossa.

Summary

A case of hemangiopericytoma arising in the meninges of a 24-year-old white man is presented. The diagnostic histologic features of this tumor and its identity with so-called angioblastic, and perhaps some chondroblastic, meningiomas are indicated.

The neoplasm grew rapidly, invaded bone, and recurred twice following operative intervention. Irradiation therapy had no clinical or morphologic effect upon its growth.

The utilization of hypothermia during the surgical removal of this highly vascular tumor greatly facilitated the operative procedure. Unfortunately, meningitis, hemorrhage, and hydrocephalus ensued, resulting in the death of this patient.

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Intraspinal Sprouting of Dorsal Root Axons

Development of New Collaterals and Preterminals Following Partial Denervation of the Spinal Cord in the Cat

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Introduction

The considerable ability of the central nervous system to adapt functionally and to compensate for a loss of neuronal tissue is well established. Several hypotheses have been presented to explain the nature of this functional recovery. Although no critical evidence has been obtained, it can be stated for the mammal, with only a few observations to the contrary (Sugar and Gerard [21] and Freeman [6]), that regeneration of severed axons is not the responsible mechanism.

The failure of severed axons to regenerate in the central nervous system does not necessarily exclude a morphological basis for the compensation, for Cajal [19] has mentioned several instances in which traumatic injury to the spinal cord and brain resulted in formation of new processes from nerve cells in the injured area. Further support for such a contention comes from the recent observations that partially denervated skin and muscle can be effectively reinnervated not only by regeneration of the severed axons but in addition by the development of new processes from the remaining intact nerve fibers (for a review, see Edds [4]). Tests for the latter phenomenon in the central nervous system have no doubt been lacking because of its functional and morphological complexity. It is now possible, however, to investigate this possibility by use of a recently developed silver technique (Nauta and Gygax [18]), which specifically stains degenerating nerve fibers of the central nervous system.

The formation of new processes from the intramedullary portions of dorsal root axons following partial denervation of the spinal cord by section of a series of dorsal roots has been described in a preliminary note (Liu and Chambers [15]). This phenomenon, referred to as collateral sprouting, has been further tested and will be presented in greater detail in the present paper. In addition, experiments were performed which revealed that partial denervation of the spinal cord by section of an intrinsic neuronal system (corticospinal tract) stimulated collateral sprouting of the intramedullary portion of the dorsal root.

Material and Methods

A total of 25 cats were used in this study. All surgery was done with the animals under pentobarbital (Nembutal) anesthesia, and aseptic conditions were maintained throughout the operative procedures.

The capacity of sprouting from an intact dorsal root, following partial denervation of the spinal cord, was tested by the following experimental procedures: 1. The spinal cord of five animals was partially denervated by unilateral section of several dorsal roots. After adequate time for removal of all stainable axon debris, a single intervening or adjacent dorsal root along with its matching root of the opposite side of the cord was severed. The animals were killed four to five days after the section of the paired dorsal roots, and the cords were stained by the Nauta silver technique (Nauta and Gygax [18]). A comparison

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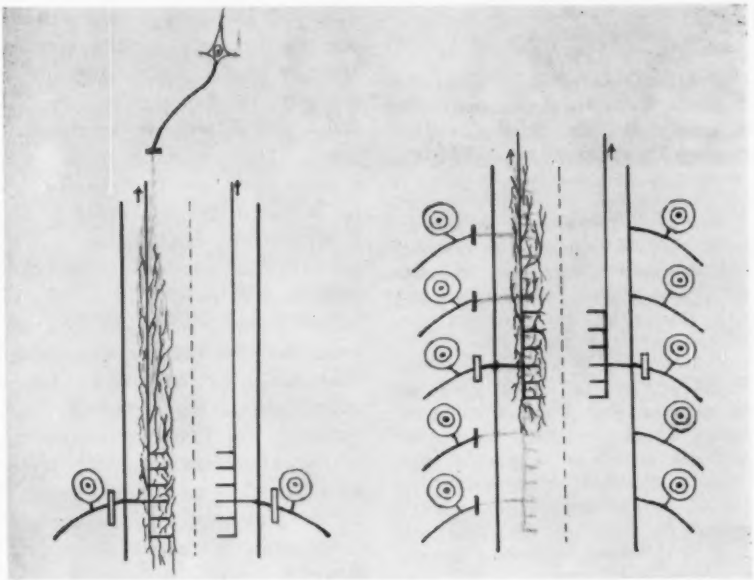

Fig. 1.—Schematic drawings to show the experimental design for detecting intraspinal sprouting of dorsal root axons following partial unilateral denervation of the cord.

Right, partial denervation of the spinal cord by unilateral dorsal root section. The severed roots and the denervated area are indicated by shaded bars and lines. The intervening dorsal root of the denervated side and the matching root of the opposite side (broken bars) were severed at a second operation. The postulated development of new processes (fine branched lines) from the collaterals of the test root on the denervated side was detected by comparing the axonal debris resulting from section of this root with that from section of the matching root of the opposite side.

Left, partial denervation of the spinal cord by unilateral section of the corticospinal tract (at cortex or bulbar pyramid). The severed tract and denervated area are indicated by a shaded bar and lines. The matching pair of dorsal roots (broken bars) were severed at a second operation. The postulated formation of new collaterals (fine branched lines) from the processes of the test root on the denervated side were detected as in drawing to right, described above.

of the extent and density of stainable axonal debris of the root on the denervated side and of that on the nondenervated side of the cord was made (Fig. 1, right). 2. The spinal cord was partially denervated in two animals by unilateral section of the corticospinal tract. One animal had a complete unilateral ablation of the anterior and posterior sigmoid gyri; the other, a unilateral section of the bulbar pyramid. After adequate time for removal of all axonal debris, a pair of dorsal roots (C8) was sectioned in these two animals. These cats were killed four days after section of the paired roots (C8), and the axonal debris of the severed dorsal root on the partially denervated side of the cord was compared with that from the root on the nondenervated side (Fig. 1, left).

It is tenatively assumed that the axonal debris resulting from section of a pair of dorsal roots in a normal animal is identical in quantity and distribution on the two sides of the spinal cord. Thus, if there is an increase in the distribution and quantity of axonal debris on the partially denervated side of the cord, sprouting of new axonal processes from the intramedullary portion of the intact dorsal root is indicated. Additional information as to the extent of sprouting was obtained by compairing the distribution and quantity of axonal debris from unilateral section of the corresponding dorsal root in the normal cat. Four cats were prepared for this purpose. Dorsal roots were sectioned extradurally and proximal to the dorsal root ganglion, and the animals were killed four to five days later. The resulting axonal degeneration was determined by the Nauta silver technique.

Thirteen animals were used to determine the period during which axonal debris persists in the central nervous system. Six of these cats had dorsal roots sectioned. Six cats had a dorsal quadrant section at various levels of the spinal cord, and in one 3-day-old kitten the spinal cord was hemisected at T9. These animals were killed at intervals of 4 to 270 days. The complete re-

moval of axonal debris was determined by the lack of any specific staining with the Nauta silver technique.

The dorsal roots to be cut were localized in relationship to the dorsal spinal processes, as described by Krieg et al.[13] The lateral side of the vertebral column was opened at the desired level, and the dorsal root was visualized by enlarging the intervertebral foramen with small rongeurs. The dural sheath of the root was grasped with fine forceps, and the root was sectioned with iridectomy scissors, just proximal to the ganglion. This procedure was found to produce no spinal cord damage, such as that which usually occurs after laminectomy and opening the spinal dura (Liu[14]).

The animals were killed by a perfusion method (Koenig et al.[12]), and the entire brain and spinal cord were removed with all the spinal nerves attached, so that the dorsal roots which had been sectioned, as well as the different spinal segments, could be identified. After refixation of the tissue in 10% neutral formalin for at least a week, representative levels of the spinal cord were prepared in cross and longitudinal sections, and these sections were stained by the silver technique of Nauta and Gygax,[15] as modified by Chambers et al.[1] This stain selectively impregnated degenerating axoplasm in the central nervous system.

Results

I. *Time Required for Disappearance of Axonal Debris.*—The time required for all of the silver-stainable axonal debris to disappear from the central nervous system after section of dorsal roots or intracentral axons was determined from 12 adult cats and 1 kitten (Table 1). In six animals dorsal roots (T10-Ca7, four cats; T11-Ca7, two cats) were sectioned unilaterally. These cats were killed, respectively, 29, 37, 61, 90, 128, and 196 days postoperatively. In six animals the spinal cord was sectioned unilaterally in the dorsal quadrant, and these cats were killed on the 7th, 14th, 21st, 105th, 261st, and 270th postoperative day, respectively. The remaining animal studied was a kitten with the cord hemisected on the 3d postnatal day and killed 77 days later.

Microscopic examination of longitudinal and cross sections of the spinal cords of the adult cats revealed that the silver-stainable axonal debris persisted in the central nervous system for 196 days and had completely disappeared by 261 days. The stainable axonal debris was gradually reduced in quantity. The first clear reduction occurred in the white matter at 29 days, and no stainable debris was found there at 128 days. In the gray matter of the spinal cord the disappearance of axonal debris was a much slower process. The debris at 196 days was greatly reduced, but still was considerable. However, no stainable axonal fragments were present at 261 and 270 days.

A comparison of the spinal cord sections from all of the adult cats revealed that there is no pronounced difference in the rate of disappearance of axonal debris following section of the intramedullary dorsal root, corticospinal, dorsal spinocerebellar, rubrospinal, and propriospinal axons.

Microscopic examination of the silver-stained sections of the hemisected spinal cord of the kitten revealed a complete disappearance of axonal debris at 77 days. There was some gliosis, which was, however, less marked than in the adult cats.

TABLE 1.—*Persistence of Silver-Stainable Axonal Debris in the Spinal Cord*

Experimental Cat No.	Lesions	Survival Time, Days	Segments of Cord Studied	Presence of Stainable Debris	
				White Matter	Gray Matter
38	Dorsal quadrant section at T4	7	C5, T4, L2	+++	+++
1	Dorsal quadrant section at T12	14	C1	+++	+++
54	Dorsal quadrant section at C4	21	T5	+++	+++
68	Dorsal rhizotomy T10-Ca7	29	L3	++	+++
91	Dorsal rhizotomy T11-Ca7	37	Various levels	++	+++
88	Dorsal rhizotomy T10-Ca7	61	Various levels	++	++
96	Dorsal rhizotomy T10-Ca7	90	C1, T13	+	++
100	Dorsal quadrant section at T12	105	Above and below lesion	+	++
67	Dorsal rhizotomy T11-Ca7	128	C1, L2, L3	—	+
93	Dorsal rhizotomy T10-Ca7	196	C1, T13	—	+
19	Dorsal quadrant section at T12	261	C2	—	—
40	Dorsal quadrant section at T4	270	C1, C2, T5	—	—
108 *	Hemisection at T8	77	Various levels	—	—

* Kitten operated on third postnatal day.

The rate of disappearance of axonal debris can be correlated with a number of factors. The debris disappears faster in the white matter, where the degenerating fibers are generally larger and more concentrated. The axonal fragments disappear more slowly in the gray matter, where the degenerating processes are smaller and generally less concentrated. Finally, the glial proliferation was considerably greater in the white than in the gray matter.

After having determined the time required for removal of all axonal debris from the spinal cord, experiments were performed to determine whether collateral sprouting of intact intramedullary dorsal root axons follows partial denervation of the spinal cord. The partial denervation was "limited" to one side of the cord by unilateral section of a series of dorsal roots in one experimental group and by the unilateral section of the corticospinal fibers above the level of their brain-stem decussation in the other group. In both groups a selected pair of dorsal roots was severed, and the resulting degeneration on the denervated and the nondenervated side of the cord was compared.

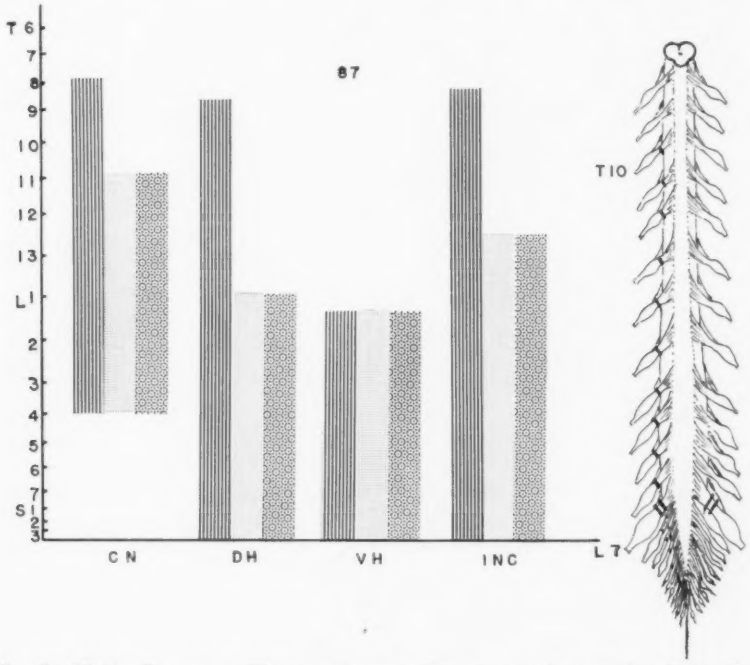

Fig. 2.—Right, diagram to illustrate the experimental procedure employed for Cat 87. First, an extensive unilateral dorsal rhizotomy (T10 to L6 and S1 to Ca7) was performed to partially denervate the cord. These severed roots are indicated by a thin line bisecting each root. In a second operation, 277 days later, a pair of dorsal roots (L7), marked by a bisecting double line, were severed. The cat was killed four days later, and the spinal cord was stained by the Nauta technique.

Left, a graph of the axonal debris shows the distribution in the spinal gray matter of the processes from the right and left dorsal roots L7 of Cat 87 after the experimental procedure shown in diagram at right, described above. The distribution of the dorsal root in a normal cat is also plotted for comparison. Minor differences of distribution (1 to 2 mm.) are not indicated in this Figure or in Figure 6.

Vertical lines: Distribution of dorsal root L7 of Cat 87 (denervated side).

Dots: Distribution of dorsal root L7 of Cat 87 (nondenervated side).

Flowers: Distribution of dorsal root L7 of normal cat.

Abbreviations: *C. N.*, Clarke's nucleus; *D. H.*, dorsal horn (central portion); *V. H.*, ventral horn; *I. N. C.*, intermediate nucleus of Cajal.

Segments of cord are numbered on the left side of the graph.

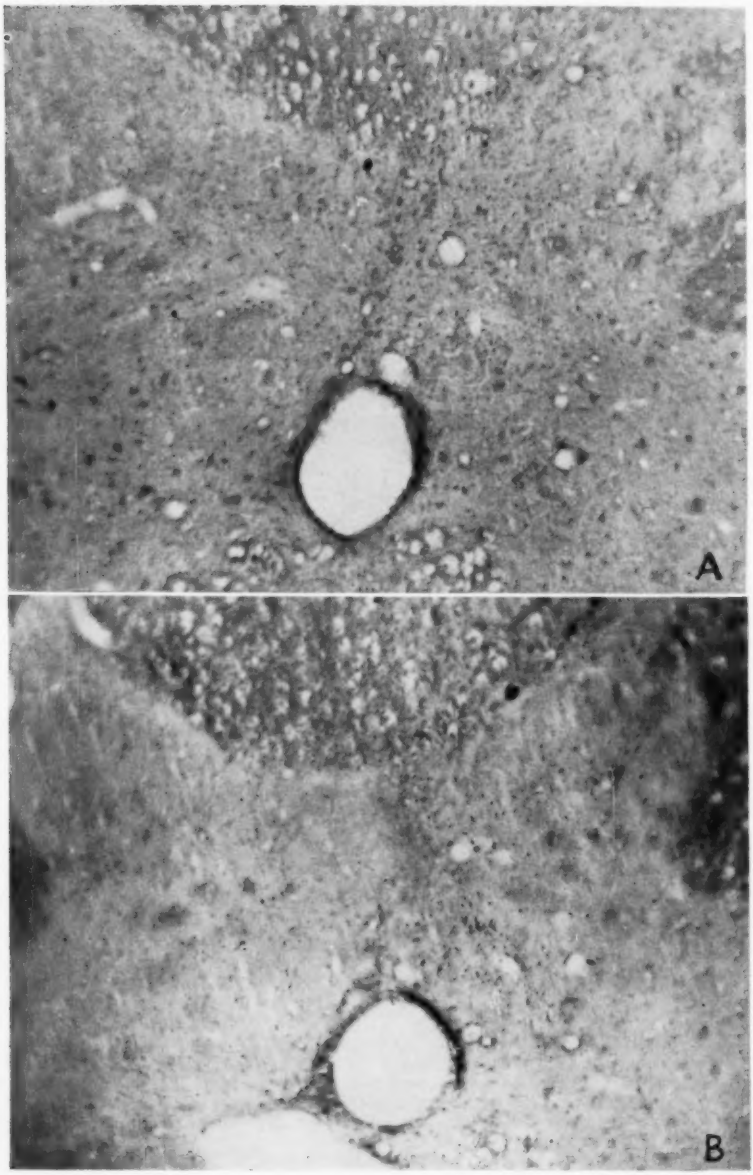

Fig. 3.—Photomicrographs of cross sections of spinal segments T8 (*A*) and T9 (*B*) from Cat 87, killed four days after bilateral section of dorsal root L7. Note that the axonal debris, which appears as black droplets and is indicated by an arrow, is limited to Clarke's nucleus on the experimental side (right side of Figure). All photomicrographs illustrating this paper were taken with a 10 × objective and 5 × ocular. Modified Nauta stain; total mag. × 72.

II. *Sprouting Elicited by Dorsal Root Section.*—A series of selected dorsal roots were sectioned unilaterally in four adult cats, and 277 to 303 days later, after removal of all axonal debris, an adjacent or interposed dorsal root was sectioned, along with its matching root of the opposite side. The animals were killed four to five days later, and the spinal cord was prepared for histological examination. One 3-day-old kitten was similarly prepared, except that the pair of test dorsal roots were severed 130 days after the first operation, after all debris had disappeared (Table 1), and the animal was killed four days later. The chronically denervated side of the spinal cord will be referred to as the experimental side; the other side of the cord will be called the control side.

In all animals there was some shrinkage of the posterior funiculus and posterior horn on the experimental side. This shrinkage was most apparent in the nucleus of Clarke and in the gracile nucleus. There was gliosis on the experimental side in the same regions. The most pronounced gliosis and shrinkage occurred in the posterior funiculus. The control side revealed no detectable shrinkage or gliosis.

TABLE 2.—*Experimental Procedures Employed to Determine Effect of Unilateral Dorsal Rhizotomy on Intraspinal Axons of Intact Dorsal Roots*

Cat No.	Partial Denervation by Unilateral Dorsal Rhizotomy	Time Allotted for Disappearance of Axonal Debris, Days	Paired Dorsal Roots Severed to Determine Sprouting	Total Survival Time, Days
87	T10–L6; S1–Ca7	277	L7	281
94	T10–Ca7	303	T9	308
111	T11–L6	277	L7	281
112	T11–L6	277	L7	281
122*	T13–L6	130	L7	134

* Partial denervation was performed on the third postnatal day.

In all experiments the axonal degeneration resulting from section of the dorsal root revealed an increase in distribution of the stainable debris on the experimental side. The degenerated axoplasm also appeared denser on this side. The kitten showed similar, but less marked, changes than the adults.

The operative procedures and the experimental results of all five cats are shown in Table 2.

Fig. 4.—Photomicrograph of a longitudinal section of spinal segment T10 from Cat 87, four days after bilateral section of dorsal root L7. Note that the axonal debris is limited to Clarke's nucleus of the experimental side (right side of the Figure). The midline is indicated by arrows. Modified Nauta stain; total mag. ×72.

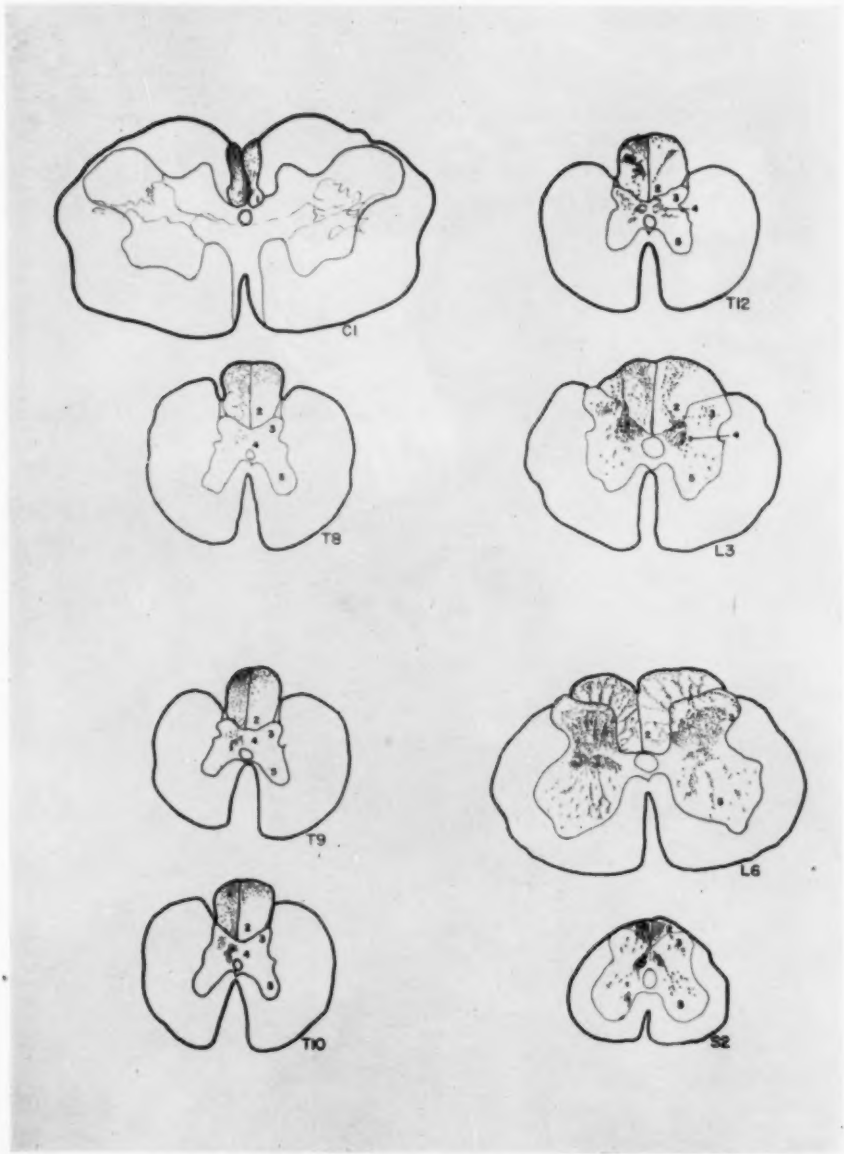

Fig. 5.—Projection drawings (×25) of representative cross sections of spinal cord of Cat 87. The left side of the spinal cord was partially denervated for 281 days by dorsal root section, and the L7 pair of dorsal roots were cut four days before the animal was killed. The relative quantity and distribution of the axonal debris from section of the dorsal root L7 are indicated by black dots. Note that the axonal debris is greater on the denervated side.

1, nucleus gracilis; *2*, posterior funiculus; *3*, dorsal horn; *4*, Clarke's nucleus; *5*, ventral horn.

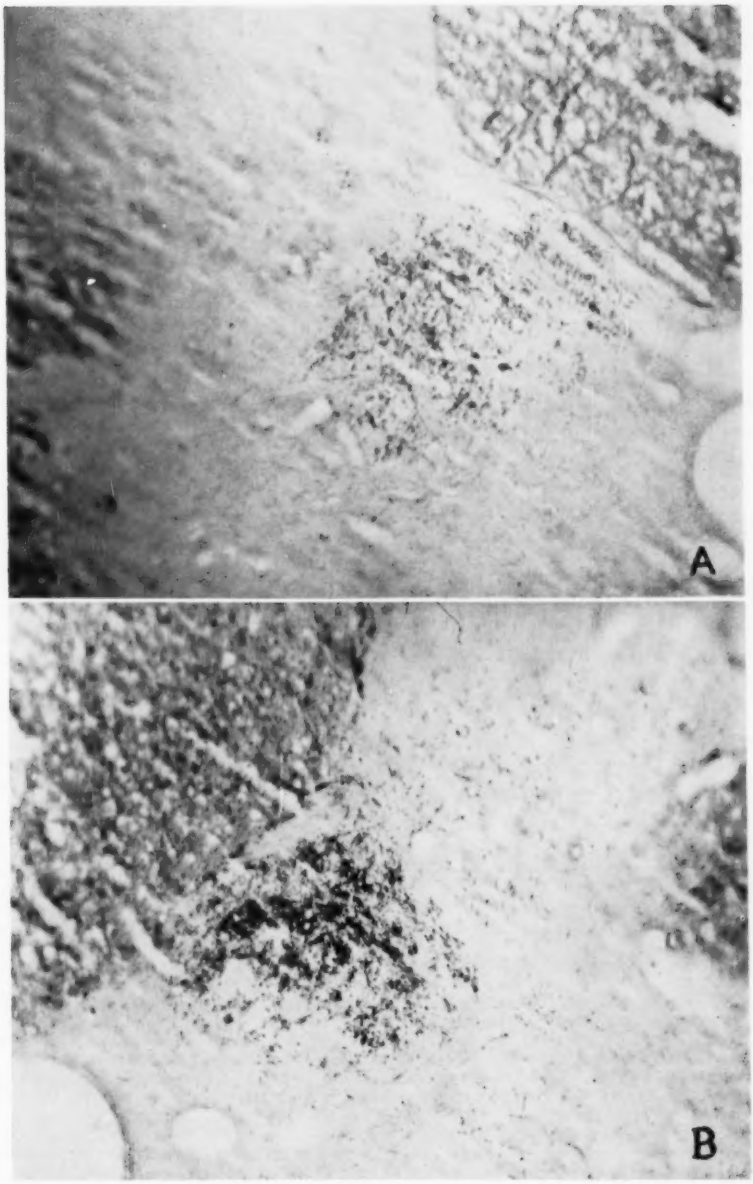

Fig. 6.—Photomicrograph of a cross section of spinal cord segment L3 from Cat 8, showing the axonal debris four days after bilateral section of dorsal root L7. It can be seen that the density of axonal debris in Clarke's nucleus is heavier on the experimental side (*B*) than on the control side (*A*). Modified Nauta stain; total mag. × 72.

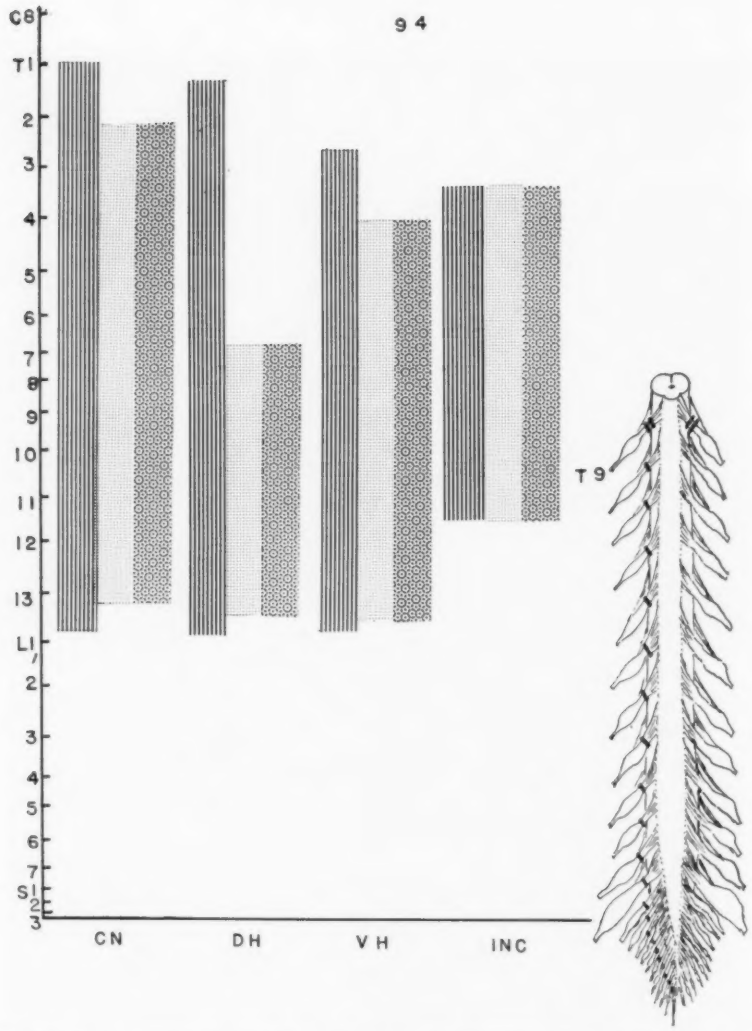

Fig. 7.—Right, diagram illustrating the experimental procedure employed for Cat 94. First, an extensive unilateral dorsal rhizotomy (T10-Ca7) was performed to partially denervate the cord. The severed dorsal roots are indicated by a thin line bisecting each root. At a second operation, 277 days later, a pair of dorsal roots (T9) were severed to test for the effect of the denervation on these dorsal root processes. These roots are marked by a bisecting double line. The animal was killed five days later, and the spinal cord was stained by the Nauta method.

Left, a graph of the axonal debris shows the distribution in the spinal gray matter of the processes from the right and left dorsal roots T9 of Cat 94 after the experimental procedure shown in diagram at right, described above. The distribution of the dorsal root in a normal cat is also plotted for comparison.

Vertical lines: Distribution of dorsal root T9 of Cat 94 (denervated side).

Dots: Distribution of dorsal root T9 of Cat 94 (nondenervated side).

Flowers: Distribution of dorsal root T9 of normal cat.

Abbreviations: *C. N.*, Clarke's nucleus; *D. H.*, dorsal horn (central portion); *V. H.*, ventral horn; *I. N. C.*, intermediate nucleus of Cajal.

Segments of the cord are numbered on the left side of the graph.

The most marked increase in the distribution of intraspinal dorsal root processes was found in Cats 87 and 94. Cat 87 had 20 dorsal roots sectioned unilaterally, 10 roots above and 10 roots below dorsal root L7 (Fig. 2, right), and the intact dorsal root L7 on this side, with its matching root of the opposite side, was severed 277 days later. A comparison of the distribution of the stainable axonal debris from section of the paired dorsal roots (L7) revealed that the axonal debris from dorsal root L7 on the experimental side occupied several segments more in the dorsal horn than did the axonal debris from the root on the control side (Fig. 2, left). The increase of debris in the dorsal horn, on the experimental side, was six segments in the central part, three segments in Clarke's nucleus (Figs. 3*A* and *B*, and 4), and four segments in the intermediate nucleus of Cajal. There was no obvious difference in distribution of the axonal debris in the ventral horn on the experimental and the control sides. However, in most levels of the gray matter there was an increase in the density of the debris on the experimental side (Figs. 5 and 6). In the posterior funiculus the experimental side revealed an increase in the amount and distribution of axonal debris.

Cat 94 had 21 dorsal roots sectioned unilaterally (T10-Ca7), and on the 303d postoperative day the ninth thoracic dorsal root was sectioned bilaterally and the animal was killed five days later. The axonal debris from the degenerating fibers of the dorsal root (T9) of the experimental side was clearly greater in extent and density than that of the control side (Fig. 7). It should be noted that there was an increase in distribution of debris in the ventral horn of two segments on the experimental side, whereas in Cat 87 there was no difference in distribution in the ventral horn of the control and that of the experimental side (Fig. 2, left). The lack of any obvious increase in distribution of debris in the intermediate nucleus of Cajal in Cat 94 and a four-segment increase on the experimental side in Cat 87 constitute another difference between these two animals.

III. *Sprouting Elicited by Intracentral Pathway Section.*—The observation that dorsal root section induces adjacent and/or intervening intramedullary portions of intact dorsal roots to develop new processes raised the question as to the specificity of the stimulus. We have observed that sprouting can also be induced in the intramedullary portions of intact dorsal roots by intracentral pathway section.

Two animals were used to test the effect of partial unilateral denervation of the spinal cord by intracentral tract section upon intraspinal distribution of dorsal root axons. In one animal the corticospinal tract was partially sectioned at the cortex (unilateral anterior and posterior sigmoid gyrectomy), and in the other animal the bulbar pyramid, at the level of the trapezoid body, was sectioned unilaterally. Both animals subsequently had the eighth cervical pair of dorsal roots cut and were killed four days later. In the animal with cortical ablation the dorsal roots were sectioned 4 years and 30 days after the first operation, and in the animal with the pyramid section the roots were severed 3 years and 30 days later.

The spinal cord of both animals showed gliosis and slight shrinkage in the lateral funiculus on the side opposite the sensorymotor cortex ablation and pyramidal section. The apex of the posterior horn was moved ventrally and laterally toward the gliosed region previously occupied by the corticospinal tract.

A comparison of the axonal debris, following the section of the dorsal roots of two sides, revealed that there was an increase in distribution and quantity of the stainable debris on the side opposite the cortical ablation and pyramidal section. The most marked difference was found in the animal with section of the bulbar pyramid. This difference agrees with the observation that section of the bulbar pyramid results in greater denervation of the spinal cord than sigmoid gyrectomy (Walberg and

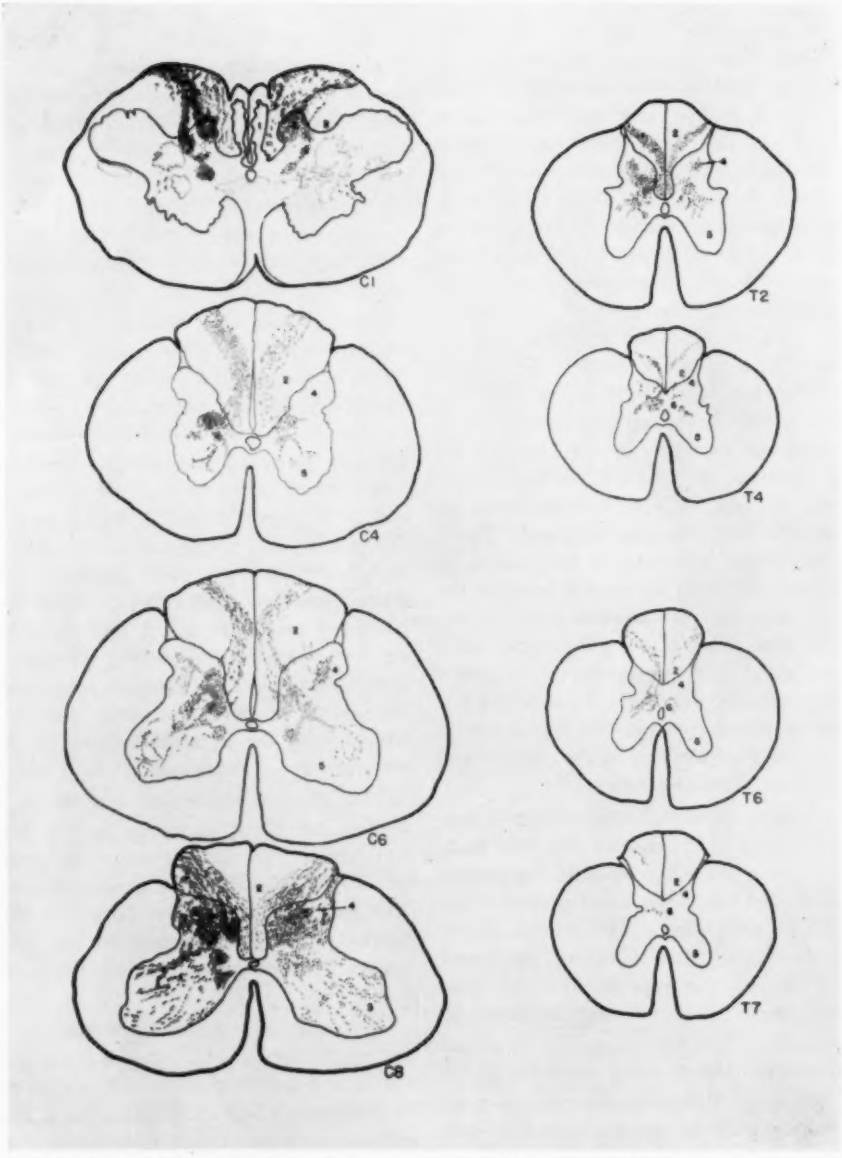

Fig. 8.—Projection drawings (× 25) of representative cross sections of the spinal cord of Cat CT2. The left side of the spinal cord was partially denervated for 3 years and 34 days by section of the right bulbar pyramid, and the eighth pair of cervical dorsal root were severed four days before the animal was killed. The quantity and distribution of the silver-stained axonal debris of the eighth cervical pair of dorsal roots is indicated by black dots. Note that the axonal debris is greater on the denervated side.

1, nucleus gracilis; *2*, posterior funiculus; *3*, nucleus cuneatus; *4*, dorsal horn; *5*, ventral horn; *6*, Clarke's nucleus.

Fig. 9. — Photomicrograph of a cross section of spinal segment T4 from Cat CT2, showing that the axonal debris (four days after bilateral section of dorsal root C8) was greater on the experimental side (left) than on the control side. The axonal debris appears as fine black granules, most clearly seen in the region of Clarke's nucleus. Modified Nauta stain; reduced to 90% of mag. ×72.

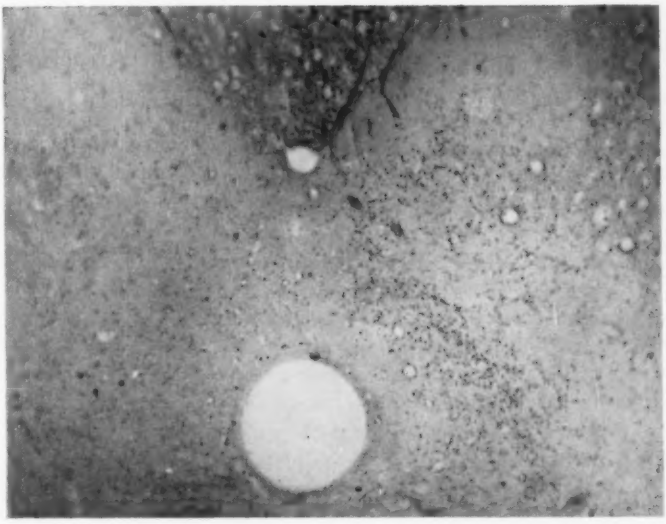

Fig. 10. — Photomicrograph of cross section of spinal segment T11 of Cat 114, which had a series of dorsal roots (T10-Ca7) severed on the left side. The right dorsal root T11 was sectioned 277 days later. It can be seen that the axonal debris is entirely limited to the right side of the cord (side on which a single dorsal root was cut). Nauta stain; reduced to 90% of mag. ×72.

Brodal[23]). The differences in distribution and quantity of the dorsal root axonal debris at representative levels of the spinal cord are indicated in Figure 8. There was an increase in the quantity of axonal debris in the posterior funiculus and gray matter on the side opposite the pyramidal lesion. An increase in the distribution of the degenerated debris was also apparent on this side. The greatest difference in distribution was noted in the gray matter of the thoracic spinal cord from T4 to T8 (Figs. 8 and 9); in the seventh and eighth thoracic segments the axonal debris was limited to the side opposite the pyramidal section.

Less marked, but similar, findings were noted in the animal with unilateral sigmoid gyrectomy. There was only an equivocal increase of debris in the upper cervical segments on the side opposite the cortical lesion, but a clear increase in quantity and distribution of axonal debris was noted on

this side in the lower cervical and upper thoracic segments (T4-T7).

It was not possible to establish from the above experiments whether or not unilateral denervation of the spinal cord stimulates only the axons of that side to sprout or involves the axons of the opposite side as well. The following experiments indicate that sprouting occurs only on the denervated side.

One adult animal, Cat 114, had 21 dorsal roots severed unilaterally (T10-Ca7), and 277 days later a single dorsal root, T11, of the opposite side of the cord was sectioned. This cat was killed four days after the second operation. Microscopic examination of the spinal cord revealed that the axonal debris was limited to the side of the cord on which the single dorsal root, T11, had been severed (Fig. 10). It was apparent that the extensive denervation of the opposite side of the cord had not stimulated this root to sprout across the midline. However, this root may have shown some sprouting without having crossed to the other side of the cord. That sprouting does not occur on the nondenervated side of the cord was suggested by the following observation: In four cats with a single dorsal root sectioned (L7, two cats; T9, one cat; C8, one cat), the resulting axonal debris was almost identical in distribution and quantity with that observed on the nondenervated side of the experimental Animals 87, 94, (Figs. 1 and 6), and CT2.

Comment

The experiments reported in this study indicate that the intraspinal processes of intact dorsal roots react to unilateral denervation of the spinal cord by the outgrowth of new axonal processes. The formation of new processes from intraspinal axons of the dorsal root fibers is apparently similar to that reported for the peripheral process of dorsal root neurons (Weddell et al.[25]). This outgrowth is referred to as sprouting and, as in the case of peripheral nerve fibers, occurs along the course of the axons, as well as at the preterminal regions (Hoffman[10]). This phenomenon of collateral sprouting has been most extensively studied in the peripheral processes of the skeletal motor neurons (Edds[4]) and has been recently described as occurring in the preganglionic fibers of the superior cervical sympathetic ganglion (Murray and Thompson[17]). The sprouting occurring at the peripheral and intraspinal portions of dorsal root neurons, at terminals of somatic motor neurons, and in preganglionic sympathetic neurons indicates that this is a general phenomenon of all neurons, and therefore collateral sprouting can be anticipated in the axonal processes of purely intracentral neurons.

It must be recognized, however, that the interpretations made in our paper rest upon certain assumptions: 1. The axons of certain groups of neurons have within the spinal cord a bilaterally symmetrical distribution, and any changes occurring in the distribution of the axons of the partially denervated side can be detected by a comparison with that of the unaltered side. 2. The distribution of the axonal processes in the central nervous system can be reliably determined by axonal section and specific staining of the degenerating debris by the method of Nauta.

The intraspinal processes of the dorsal root neurons were selected for this study, as they can be sectioned extradurally without traumatizing the spinal cord (Liu[14]).

The distribution of the spinal processes of a selected pair of dorsal roots, as determined by the method of specific impregnations of axonal degeneration, revealed that the dorsal root axonal processes on the partially denervated side of the cord occupied a greater area and were denser than those on the intact side. The distribution of a given dorsal root on the nondenervated side of the experimental animal (Liu[14]; Figs. 2 and 7 of the present paper), provided it makes the same contribution to the innervation of the limbs (Romanes[20]), was found to be nearly identical in the normal cat with the distribution in the control side of the experimental animal.

Thus it would appear that our method of determining sprouting is valid and that only the intraspinal processes on the denervated side of the cord are stimulated to sprout. The amout of sprouting appeared to be determined by the extent of the denervation. It was greatest in those regions which show most degeneration following dorsal root section (Liu [14]) and pyramidal section (Chambers and Liu [2]). However, some sprouting of the dorsal root axons in regions having slight or no degeneration was also apparent in the animals with pyramidal section (Clarke's nucleus, ventral horn, and posterior funiculus).*

From our results, the stimulus to sprout would appear to be confined chiefly to the regions of degeneration, and this observation is further substantiated by the fact that extensive unilateral degeneration of the spinal cord does not cause the dorsal root axons of the nondenervated side of the cord to sprout (Cat 114; Fig. 10). The latter observation agrees with the finding of Edds [5] that unilateral denervation of the diaphragm does not stimulate sprouting from the intact axons of the nondenervated side. In both cases, spinal cord and diaphragm, this failure to sprout across the midline is probably not due to a physical barrier and may represent some specificity of terminal fields or of degeneration products. This apparent specificity could be further tested in relation to the gracile and cuneate nulcei, for there is no known normal overlap in dorsal root supply to these nuclei.

The stimulus to induce the collateral sprouting in the peripheral nervous system has been considered to be due to a number of factors (Edds [4]). The present paper has little to offer in this matter, except that it would appear that the mitotic proliferation of Schwann cells is not a factor. They are lacking in the central nervous system and their counterpart, the glial cells (oligodendroglia), increase by amitotic division rather than by mitosis. The suggestion of Hoffman [9] and of Hoffman and Springell [11] that the degeneration products of myelin are the effective stimulus may serve to explain the present observations.

That the new-formed collaterals from a given dorsal root occupies but a relatively slight area of the degenerated regions may be due to several factors. 1. The intramedullary axons may possess only a slight capacity for forming new processes. 2. The environment of the central nervous system may not be favorable for the development and/or maintenance of new processes. This sprouting, on the other hand, may have appeared to be less than it really was, for adjacent dorsal roots, as well as intracentral neurons, may have sprouted into the degenerated area and would not have been detected by this method. However, that there is a failure to restore the normal number of fibers to a region could be seen by the shrinkage in volume and the marked reduction in the neuropil of certain nuclei (gracile and Clarke's nuclei).

The observation that intact intraspinal root axons can be stimulated to form additional collaterals following partial denervation of the spinal cord suggests that these fibers, like those of the peripheral neurons,

* Two other possible interpretations for the increase in distribution and quantity of dorsal root axons following unilateral denervation of the cord should be considered in addition to sprouting. The first is related to the possible effects of a glial reaction in altering the degeneration and staining of the dorsal root axons. The second is based on the possible maturation of normally occurring fine, or even submicroscopic, branches of the dorsal root axons (Fernández-Morán [21]), which, if stimulated by denervation to increase in size, may then be stained and visualized following degeneration. Both these possibilities cannot be critically evaluated from the results of the present or other studies. However, the influence of the glial reaction can be minimized by the observation that an increase in the dorsal root axonal debris was seen in some instances without any accompanying gliosis (i. e., in the posterior funiculus following unilateral denervation of the spinal cord by pyramidal tract section). Further, the time allotted for determining degeneration in the present study is probably optimal for the complete staining of degeneration of the dorsal root axons in the cat by the Nauta technique (Glees and Nauta [7]; Liu [14]; Chambers and Liu [2]).

have a dynamic association with the structures they innervate. No attempt was made in the present study to determine the physiological significance of the new collaterals. In fact, it must be emphasized that the staining technique employed in this study does not reveal the synaptic terminals (Glees and Nauta [7]), and therefore any statement as to the ultimate association of the new processes is based on inference.

However, the anatomical findings, limited as they are, support the contention that morphological changes of intact axons may play a significant role in the compensation which follows injury to the central nervous system. Recent physiological observations by McCouch and co-workers [16] in the cat and monkey with a chronically hemisected spinal cord are particularly pertinent to this hypothesis. They observed that the presynaptic dorsal root potentials, elicited by stimulation of matching dorsal roots below the level of hemisection, were greater on the hemisected side of the cord. They have suggested that the loss of spinal synaptic connections by severing descending pathways is restored by the development of additional new endings from the dorsal root axons and that this process can account for the recovery of spinal reflexes.

The observations of Teasdale and Stavraky [22] may be explained by a similar sprouting of the corticospinal axons. They deafferented one hindlimb in a series of cats and found that after four days the deafferented limb had a lower threshold of excitability, as compared with the normal limb, to stimulation of the basis pedunculi.

Finally, the gross morphological changes in the axonal processes observed in the present paper, along with the histological evidence of Weber [24] that the synaptic terminals are labile structures, make more credible the hypothesis that learning requires a slight morphological change in the terminals (Hebb [8]; Eccles [3]).

Summary

Morphological evidence is presented that the intact intraspinal processes of spinal sensory neurons of the cat react to partial denervation of the spinal cord by the formation of new processes. This phenomenon is similar to that which has been described in the peripheral processes of sensory, motor, and preganglionic sympathetic axons. It is postulated that intrinsic neurons of the central nervous system will react similarly.

The development of new collaterals and preterminals following partial denervation of the spinal cord is discussed in relation to the reflex recovery from spinal shock, and it is suggested that this phenomenon may be part of the mechanism by which the nervous system functionally adapts to injury.

The method for producing and detecting the formation of new processes from the intraspinal dorsal root axons is as follows: 1. The spinal cord is partially denervated unilaterally by section of a series of dorsal roots or by corticospinal tract section. 2. After disappearance of the degeneration products from the denervation, a matching pair of dorsal roots, one on the partially denervated side and one on the nondenervated side of the cord, are severed. 3. The animals are killed four to five days after section of the matching roots, and representative levels of the spinal cord are stained by the Nauta technique for degenerating axoplasm. 4. The degeneration products are compared on the denervated and the nondenervated side of the cord.

In all experiments a comparison of degeneration products on the two sides of the cord reveals an increase in distribution and quantity of the stained axonal debris on the denervated side.

Mrs. Chung-Yu Liu gave technical assistance.

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News and Comment

ANNOUNCEMENTS

The Hofheimer Prize.—The Hofheimer Prize of $1500 is awarded annually by the American Psychiatric Association for an outstanding research contribution in the field of psychiatry or mental hygiene which has been published within three years of the date of the award. The competition is open to citizens of the United States and Canada not over 40 years of age at the time the article was submitted for publication, or to a group whose median ages do not exceed 40 years of age. The next award will be made at the Annual Meeting of the Association in May, 1958. Articles submitted to the Prize Board before March 1, 1958, will be considered. Eight copies of each publication and data concerning age and citizenship should be sent to John I. Nurnberger, M.D., Chairman, Hofheimer Prize Board, 1100 W. Michigan St., Indianapolis 7.

Psychological Reactions of the Aged in Surgery

The Reactions of Renewal and Depletion

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The illnesses requiring surgery are among the most strenuous adversities of aging. The decision to operate upon an elderly person must take into account the stress the experience will imposed upon the cardiovascular, metabolic, and other systems which, with less resiliency than in earlier years, will have to adapt to the effects of anesthesia, tissue damage, and the strain of postoperative restoration of somatic function. The surgical experience is also a threat to the integrity of the aging nervous system and to the elderly patient's psychological adaptation. Our research team has had the opportunity of intensive observation of a number of aged people who became ill and were admitted to a surgical service for treatment. We have assembled data that contribute to an understanding of the psychological responses of the aged person to surgery.

Concentration upon the psychologically stressful aspects of surgery from a perspective of the therapeutic value of surgery has not led us to conclude that surgery should be discarded as a treatment for an ailing and aging person. Our findings do not provide opposition to surgery, any more than do discoveries of the special problems of electrolyte balance in the pre- and postoperative periods of the elderly patient. The stress incident to any therapy poses problems for consideration rather than indicating that such stress must always be avoided.

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Material and Methods

The study has included 45 patients, all 65 years or over, admitted during 12 months (1953-1954) to the surgical service of the Cincinnati General Hospital. The means of selection of these patients was as follows: They were included by chance in the random selection of a total of 200 surgical patients chosen for the purpose of a more general and extensive study of the psychological aspects of surgical illness and the representative surgical patient. The larger group, of 200, proved at the end of the year of the study to be statistically representative of the 3656 admissions during the same year with respect to age, race, sex, duration of stay in the hospital, whether or not operation was performed, site of operation, and whether surgery was elective or emergency. In summary, patients were randomly selected from all surgical admissions rather than for special characteristics, and the 200 patients truly represented the year's total surgical admissions.[1] The 45 elderly patients from whom were derived the findings of this report include all of the persons of 65 or over who happened to be picked by our random selection method. There is reason to believe, therefore, that this subgroup is representative of the patients of 65 and over who enter a municipal hospital for surgery.

TABLE 1.—*Composition and Group Characteristics of Surgical Patients Aged Sixty-Five and Over*

Total patients	45
Male	30
Female	15
Mean Age, Yr.	73.2
S.D.	6.4
Range	65-90+
Marital Status	
Married	13
Single	7
Widowed	21
Separated	1
Undetermined	3
Race	
White	29
Negro	16
Duration of stay	
1–15 days	19
16–30 days	6
Over 30 days	20

The procedure and method of the study after selection of the subjects have been previously described in detail.[1] Immediately after selection, the patients were seen in the first of a series of psychiatric interviews which continued almost daily until discharge. The name of a close relative or friend was obtained, and this informant was interviewed by a social case worker for background and corroborative or contradictory material. Projective and other psychological tests were administered sometime during the stay in the hospital. Whenever possible, a follow-up psychiatric interview was arranged three to six months after discharge, and the case worker repeated his interview with the informant. There was care during the study to avoid interference or participation in the treatment of the patient.

Results

The composition and group characteristics of the surgical patients of 65 and over are summarized in Table 1. The ratio of men to women was 2:1 in this group of aged patients. When the patients were placed in their general diagnostic categories, the specific diagnostic areas for this predominance became clear. Men exceeded women in genitourinary illnesses by six. In the illnesses affecting the extremities, including fractures, peripheral vascular disease, and amputations, men exceeded women by nine. The sum of these two categories, 15, exactly accounts for the excess of men over women in the group of 45. The sexes were about equally distributed (49% men, 51% women) among the 200 surgical patients, and the excess of women over men under age 65 was accounted for by the numbers admitted for gynecologic illness. We were able to obtain follow-ups, at an interval three to six months after discharge, in 60% of the subjects of this study of patients of 65 and over. Three patients (6.7%) died in the hospital, while six (13.3%) died before follow-up could be arranged. The remaining 20% completely refused further contact, disappeared, or died without notice reaching us. Almost without exception, these elderly surgical patients were from the lower socioeconomic strata of Cincinnati.

Organic Psychoses in Aging Surgical Patients

It is conceivable that, as medical science extends the life span, we may be entering an era in which we shall be able to maintain the function of the heart, lungs, and other parts of the body well beyond present expectancy. Such advances, however, could mean a marked increase in the mental disturbances of senility, and, ironically, while retaining physical health, too many would spend the last of their days with seriously impaired mental capacities. The psychoses of senility have until now had an aura of inevitability and relentless progression. Successful specific treatment for the full-blown form of senile and cerebral arteriosclerotic psychotic reactions has not yet been described. Some measures of preventive value, however, may emerge from further understanding of the factors that precipitate the onset of these reactions. For example, hospitalization and varying forms of surgical and medical treatment are frequently associated with the onset of aggravation of the mental deterioration that features these psychoses. Experience suggests not only that it is the physical or metabolic ordeal which stiffens and decreases the lumen of the cerebral arterioles but that the changes arise from diverse and combined aspects of the over-all experience of an illness in the later years. Separation from home and loved ones, fright, and fearful surrender and resignation are some of the forces brought to bear upon the older person entering a hospital. Clinicians have

frequently observed an elderly acquaintance, who, admitted to the hospital for even a mild ailment, suddenly begins deteriorating in several directions simultaneously. Frequently it has happened that the patient was admitted for treatment of an uncomplicated hernia, and soon cardiovascular decompensation appeared along with respiratory disease and memory and alertness began to slip. It has often been said about such patients, "He just seemed to fall apart." Later the clinician may recall that before all of these events took place the elderly patient had been apprehensive, depressed, and confused in the new surroundings of the hospital. Our data throw some light upon the factors that seem to accelerate central nervous system and psychological aging in the hospital patient.

Eleven patients showed progression of deterioration, all requiring institutionalization or special nursing care.

The average age of those elderly patients who suffered a progression of mental deterioration in the hospital exceeded the average age of those who did not by 6.4 years, approximately one standard deviation. This difference in means is significant at the 1% level. However, the significance of differences, though suggesting an important etiologic factor, does not indicate a sparing of the lower age groups, nor does this finding settle the question of etiology, since there were many of a comparable age who escaped progression of mental deterioration.

An acute organic psychosis preceded the development of chronic deterioration in 7 of the 11 patients. Observations of this process brings one to the hypothesis that, once the balance was tipped toward delirium, most elderly persons were not able to return to their former level of integration. The changes during the development of the delirium that ends in chronic deterioration occur in three stages: a prepsychotic stage, the acute delirium, and the chronic brain syndrome stage. These alterations may be conceived as the phases of a process of adaptation, a striving toward a steady state of homeostasis. It may be assumed that the stress imposed at the beginning of the hospital course was greater than the integrative capacity of the patient, and that the prepsychotic disturbance is the disruptive effect of the emotional and physiologic stresses. The delirium represents an overwhelming of the adaptive capacities, and finally the new equilibrium is reached at a lower, more regressed level in the phase of chronic deterioration. In almost every instance it was observed that the patient was first apprehensive and deeply depressed; then, as anxiety mounted, confusion entered, and the delirious state became full-blown. This phase is the one of total disruption of integrative capacity. The patients emerged from the agitation and turmoil of delirium to a phase of comparative serenity, a chronic organic psychosis, in which they were regressed, out of contact and, in a sense, had submitted to the process of disintegration to reach equilibrium at a different level.

TABLE 2.—*Incidence of Progression of Mental Deterioration During Hospital Stay*

A.	Total with progression of mental deterioration	11
	Male	8
	Female	3
	Negro	6
	White	5
	Mean age*	77.8
	S.D.	6.05
	Mean age* of those not showing deterioration	71.4
	S.D.	6.5
	t	3.04
B.	No. of patients with indication of deterioration before admission	23
C.	Number of patients in (B) with psychotic reactions before admission	2

* Difference between mean ages of groups with and without deterioration is significant at 1% level.

The diagnoses for which these 11 patients were admitted and the treatment they received did not distinguish the group except that they had three out of the four amputations of the lower extremities on patients 65 and over. These procedures were performed for treatment of peripheral vascular complications.

In all cases in which progression of mental deterioration occurred during hospitalization, there was ample opportunity to assess the psychiatric and social status of the patients prior to their downhill course. Our

impressions of the degree of psychological or emotional disturbance were recorded before we knew that the patients were to present a progression of deterioration. In 9 of the 11 cases there was very severe depression, anxiety, easy irritability, or paranoid disturbance, starting before or very shortly after admission to the hospital. Our data appear to make clear an association between preceding severe "functional" disturbances and the later development of organic psychoses. These symptoms were occasionally seen in the patients who did not develop a progression of mental deterioration, but without the consistent severity of the cases in point.

Case 179 seemed in early interviews to epitomize an adaptation to aging that would be graded as most successful by the majority of psychiatric workers in the problems of the senium. He was a spare and wiry, sandy-haired man, who was charmingly garrulous, and usually alive with anecdotes and sagacious advice. He had retired as a machinist about four years before admission but remained active via an interest in "inventions," actually, ingenious motorized toys for his grandchildren. He and his wife had an intimate and devoted relationship, kept alive by their common emotional attachment to their children and much attention to several grandchildren. One year before admission the patient experienced an episode of acute urinary retention, and at that time benign prostatic hypertrophy was discovered in conjunction with urethral constriction. Some dilation of the latter constriction was attempted during the ensuing 12 months, but 3 months before admission another episode of retention occurred and a cystotomy was performed. Next, some gradual dilations were done on an outpatient basis, and, with lack of success, the patient was admitted to the hospital. Treatment consisted of the daily passing of graduated sounds, to be followed by a transurethral resection of the hypertrophied prostate. After 10 days the pain of the dilation procedures became cumulative, and the patient became apprehensive and began pleading for relief from pain. Next, he began to voice anger, which was initially direct, then displaced, and finally projected ("They hate me here"). During this change in personality he was alternately withdrawn and irascible. He reported periods of amnesia and depersonalization and on two or three occasions became overtly delirious. The latter manifestation caused the attending physician to withdraw some of the analgesic medication. By the time (six weeks) that the dilating procedure had been completed and the transurethral resection performed, the patient was a spiritless, much regressed, apathetic man. He had developed defects in remote and recent memory, was less alert, and occasionally mildly disoriented. On follow-up three months after discharge he had become even more apathetic, his only interest being a concern with bodily function. In place of talking of his "inventions," he told his children and grandchildren of his attempts to find a truss that would fit and mumbled about his bladder function. The case worker found that he had become completely inactive except for the energy required for a rocking chair. Psychiatrically, there was increased failing of mental capacity.

In summary, the patient was a fairly well-integrated elderly man, who had been living in a supporting and gratifying environment, and who was subjected by surgical necessities to arduous treatment that resulted in prolonged and relentless agony. This continuing pressure first evoked anxiety and rage, and as its disruptive effect increased, he crossed the border into a physiological brain disorder, with the changes in mental function observed on follow-up.

A final condition of possible importance in the precipitation of progressing mental deterioration in the aged patient in surgical treatment is the social and family setting from which the elderly patient was admitted. The cases in point were not in marked contrast with the total subgroup, but the factor seemed more extreme. Five of the eleven appeared to have lost acceptable and comfortable places in society more than any of the other persons in the group aged 65 and over. The living quarters of one were described by an experienced case worker as the "worst I've ever seen." Three were living alone and friendless in tiny flats, and the fifth lived in a very low-grade hotel for transients. In addition to these five patients most clearly living in unaccepting and depriving social settings were some marginal cases. The sixth came from a rest home to which he had not adapted; a seventh did not feel accepted by her sister and brother-in-law, and the remainder were admitted from homes and family settings that varied from slightly better to adequate. The patients from such inadequate social and home settings were not surrounded during their hospital stay by an emotionally supportive environment that might have been supplied by loving, solicit-

ous, and familiar relatives or friends. It is suggested by such material that the aged person's contact with reality may be more easily severed when it is socially tenuous to begin with.

Rothschild [2] reported in 1937 on a series of 29 senile psychotics studied psychiatrically and, after autopsy, neuropathologically. He summarizes his material as follows:

> In the light of the conception advocated here the pathologic changes no longer appear as the sole determining factor or even necessarily as the most important factor in the occurrence of a senile psychosis. The person's capacity to compensate for a certain amount of tissue damage becomes of immediate importance. This may represent the unknown factor that determines the occurrence of a senile psychosis. Depending on this capacity, one person with senile changes in the brain may show no clinical abnormalities, another may develop a psychosis which shows little evidence of compensatory mechanisms and between the two extremes, all gradations will be observed. . . . The inability to meet such [personal] problems successfully may be the crucial factor that destroys or greatly impairs the person's compensatory capacity.

Other workers have demonstrated that the clinical and phenomenologic picture cannot be explained by the organic defect alone. Bender [3] and co-workers, in 1938, experimented with 24 subjects manifesting the Korsakoff psychosis, using the Bender gestalt figures.

> The attempt to understand an organic defect merely as a defect is futile. The person with an organic defect is more than normally at the mercy of field forces and tendencies to organization. . . . The action of field forces is . . . determined not merely by the characteristics of the figure as such [or the defect] but by individual attitudes. . . . One deals not merely with a fading of traces but with a new type of organization of the traces.

Rosenthal [4] intensively studied 135 cases of senile psychoses in Bellevue Hospital. He found that the phenomena of senile psychoses frequently represented an individual response to overwhelming environmental factors, as well as to the defect.

With regard to the effect of anesthesia upon the brain of the aged person, a study [5] of 1193 elderly patients undergoing surgery offers inconclusive data. Relatives attested to change in mental function in one-third of this series. "Substantial evidence of brain damage" was found in 120, with 30 of this group showing "severe cerebral damage." No single factor or combination of factors could be incriminated, and the mental catastrophes did not appear to be a direct function of the anesthetic agent employed, the severity or duration of hypotension, or the extent of hemorrhage. "The patient himself, rather than any external factors, seems to hold the explanation . . . an individual susceptibility."

Our study of a small group of elderly patients undergoing surgery and then showing a progression of mental deterioration tends to confirm and extend the investigations reported above.

The factors in addition to the stress of illness, physiologic upheaval, and operation which may combine to bring about progression of mental deterioration in the the aged admitted for surgery may be summarized as follows:

1. Age appeared to be a factor. Patients in the range of 70 and over were more liable to progressive mental deterioration. Also, patients developing mental deterioration during hospitalization were significantly older than those who did not.

2. An acute brain syndrome or delirium, in response to a multiplicity of factors, proceeded to more chronic deterioration in seven cases.

3. Antecedent increase in anxiety, depression, and/or severe emotional disturbance was associated with progressing mental deterioration in 9 of the 11 patients.

4. Patients who lost an accepting and gratifying home and social setting, and who had no one to offer support and assurance during the hospital stay, were found more likely to develop a progression of mental deterioration.

Depression in Elderly Surgical Patients

> Pneumonia, friend of the aged! In an acute, short, not often painful illness, the old man escapes those cold gradations of decay so distressing to himself and to his friends.

The truth of these words of Sir William Osler in several editions of his textbook has been altered by medical progress. The

antibiotics have come between the good friends. However, with the loss of a friend, perhaps the "old man's" life has become even more bitter, for the psychological and social significance of Osler's words in modern times makes him not only discerning but prophetic.

An aspect of the situation described by Osler is the probability that the most widely disabling psychopathologic reaction in elderly patients consists of varying degrees of depression. Though a depressive mood of some intensity was suffered by 90% of our elderly patients at one time or another during hospitalization, we shall discuss here only those affective states that were in a major way disabling, such that they modified the course of illness and treatment and affected outside adjustment in a significant manner. By depression we mean the feelings of melancholy, apathy, anhedonia, severe lack of hopeful anticipation of the future, despair in one's self and environment, and despondent bitterness. Gloom and the more dramatic and turbulent forms of melancholy do not seem as common; rather, the flatter kinds of depression, with anhedonia, apathy, and bitterness, feature the affective reactions of the aged.

Depressive reactions, as we conservatively diagnosed them, appeared in 22 of the 45 patients included in this study. In two patients such reactions extended into depressive psychoses. An organic brain deterioration was imposed upon a depressive substrate in five cases. The depressive reactions were equally divided between male and female patients. The illnesses suffered and the surgical procedures did not differ significantly from those of the total subgroup except for the inclusion of four cancer patients and one overt suicide attempt.

It has not been entirely possible to separate and classify the psychodynamic factors working to produce the broad variety of depressive reactions seen in our elderly surgical patients. We cannot be sure in any case that either the more general problems of existence outside the hospital or the pressure of illness, treatment, and hospitalization has been the principal force precipitating depressive affective disturbance. In the large majority of cases the interactions of personality, environment, illness, and hospitalization have probably been responsible for the depressive consequence.

Busse [6] and the research team working with him have derived the conclusion from their study of large numbers of nonhospitalized and institutional elderly subjects from various social levels that depression in the aged arises not so much from the hostility-turned-inward-guilt dynamic as from loss of esteem, lowered status, body-image deficiencies, and inability to respond to everyday stresses. These latter dynamics cause elderly people to become "misers of their affections," and depression appears. In our cases the stresses were severe enough, or the personalities were more sensitive to stress, such that we usually observed a combination of the two sets of psychodynamic forces. In other words, in the same patient there was rage and guilt as well as loss of self-esteem and lowered status. Frequently a real defect in body image caused by illness or surgery also functioned to deepen the depression.

For example, a 68-year-old woman, admitted for possible closure of a colostomy which had been performed for treatment of diverticulitis, was originally hopeful that she would be rid of the inconvenience of the colostomy. After a week or so she was told that closure would be unlikely, but that she was to remain in the hospital for further tests. She had been adjusting to life with rigid, moralizing attitudes and moderately incapacitating, self-defeating behavior. There were severe problems at home in that she was forced to care for a husband made blind, bedridden, and aphasic by a stroke. There was a highly charged ambivalent relationship with a sister who shared the home, and there was severe economic hardship. During the hospital stay, her previous ways of self-righteousness and moralizing gave way to feelings of disgust with herself, fantasies of personal sin, and uncleanliness, in which the body image with colostomy played a role. The colostomy also contributed to a sense of inability to meet stress and signified a crumbling deterioration. With these changes, depression, soon featured principally by a pervasive apathy, became evident. The state of

apathy was in marked contrast to her previous hearty hostility and high-pitched moralizing on any issue! By the time of follow-up the depressive-apathetic state had deepened, and severe cardiac decompensation was not responding to treatment.

The case just summarized is but one illustration of the clinical and psychodynamic structure of depression among the cases we are describing. Problems of change and defect in body image, lowered status, and suffering self-esteem—in other words, the psychosocial effects of aging—appear in this case to enhance and lay bare feelings of frustration, rage, and, consequently, guilt and a turning inward of aggression. The factors that Busse describes appear to make the elderly person more prone to depression, less able to find a way out, and one cause of bitterness leads to another. The subjects of this research who were 65 and over were fully as capable as their younger fellow subjects of the mechanisms of rage toward the lost love object, guilt, and inward-turned aggression. Such consequences may have become more frequent under the pressure of the psychosocial dynamics proposed by Busse and his co-workers.

There were other factors that helped to aggravate or modify depression in the aged patient. For example, the cheerlessness and barrenness of hospital wards, the occasional impatience of hospital personnel with the old person's slow reactions and fixed habits, long periods of immobilization, and, finally, a factor that must be vaguely labeled the "death trend." [7] The last-mentioned force toward aggravated depression had its effect when the patient had lately become a widow or widower, or when old friends or relatives had recently died, and, even with some acuteness, when another elderly patient on the same ward, with whom the person had had but a few words, died. Such events stirred a feeling of abandonment, the loss of cohorts and colleagues, and then a despair about oneself.

In second place behind the organic psychoses, the depressive reactions, neurotic or psychotic, had the most corrosive effect upon psychological adaptation to aging and upon successful recovery and response to treatment of a surgical illness. While advances in surgical treatment continue, their clinical usefulness will in part depend upon the ability of society to make a better place for the aged person. Meanwhile, psychological techniques based upon awareness of the problems may improve the over-all treatment of the ailing elderly person requiring surgery.

Projection and Paranoid Reactions in the Aged

Observation of the increased use of projection as a defensive mechanism in the elderly is almost commonplace. Laymen have come to expect that, in moments of frustration, the older person will rail at the younger generation and the changing order as the cause of his difficulty. When feeling the sting of the disinterest or impatience of his children, the old man may become suspicious of their hostility, or think "they wish I were dead," or become self-righteous and accusing. Projection as a defense was similarly used by the majority of the surgical patients of 65 and over. The use of projection, extending and spreading into paranoid character trends, occasional delusional thinking, and overt paranoid psychoses, was observed in nine patients. This paranoid group of elderly patients had a mean age of 73, with 2 men and 7 women. Three of these paranoid patients developed deliria and progressed to chronic mental deterioration. Five of the nine patients presented outright delusional material, while the remainder employed paranoid ideation with a restraint that barely avoided more overt break with reality. All of these patients, with the exception of two, were severely ill. All had hazardous surgical procedures, with one exception. This fact suggests that there was a kernel of truth in the patients' suspicions that they were about to be or had been hurt. The trend of paranoid thinking in these patients began prior to the illness and treatment, and this type of thinking was simply amplified by their threatening surgical experiences. Also,

the adjustment to operation and the hospital was made considerably more difficult by the occurrence of this paranoid form of adaptation, and this constellation in all nine cases became more fixed and profound during their experience in the hospital.

A general understanding of paranoid reactions in senescence may be furthered by the formulation of the psychodynamic sequence leading to this kind of thinking in the patients we studied. In five cases the emotional atmosphere in which the patients found themselves was that of indifference.

The indifference of family, friends, in fact, of society and the world, confirmed by our social case work study was the essential condition that began the cycle. The attitudes toward oneself that a person perceives in others may be classified as love, hate, or indifference. In the case of these five patients, love as an attitude of others toward the self was not forthcoming in any discernible form from those close to the person or from anyone in the social environment. The choice remained between indifference and hate, and, being unable to tolerate as a human being, as a gregarious animal, the possibility of indifference, they compromised upon hate as the emotion and attitude others must feel for them. Their inner dialogue appeared to be: "They don't love me; they cannot be indifferent; they must hate me, want to kill me," etc.

A 69-year-old woman, a diabetic, living totally alone and incapacitated by peripheral vascular disease, had her only contact with the outside world through the busy physician who visited her biweekly. She became convinced that the medicine he left for her was poison. An 82-year-old widow, who had formerly been a strong figure, dominating and ruthlessly maneuvering her husband and children, had been largely left alone by them except for dutiful visits, probably because they had finally determined to avoid her domination. She weathered a cholecystectomy well and, though remaining clear and alert, revealed an intricate paranoid system, with both grandiose and persecutory elements in which unjust vengeance was wrought upon her.

A second mechanism, sometimes parallel and concomitant with the first, was observed also in the remaining four patients. Occasionally, the indifference, impatience with the "set" ways of the elderly, or frustration of needs for support or affection caused the elderly patients to become angry, and then guilty or fearful of further loss of love. This sequence led to expressions of self-depreciation and accusations that others did not or could not love them. Attitudes of self-repudiation were too easily transformed to feelings of persecution. The masochistic attitude, "See how you hurt me," served the wish to restore love; but, with failure and disappointment, it became "They are hurting me, want to be rid of me, do me harm," etc.

Reactions of Renewal and Depletion

In the foregoing sections we have described the most disintegrative psychopathologic reactions in the aged during the treatment of a surgical illness. We now intend a description of a psychophysiologic response to surgical treatment taking place in one direction or another in nearly all of our cases. A classification of the comprehensive, emotional and physiologic, reactions to illness and surgery in the aged includes the responses of "renewal" and "depletion."

The reaction of renewal implies that (1) the treatment had a successful outcome and the illness was cured, or arrested, but, further, that (2) the patient felt himself that there had been repair, that he was as well or better fitted to carry his responsibilities, to meet stress and continue activity, and that (3) the attitude of renewal would then function as a psychodynamic force, leading to feelings of hope, independence, more freedom of expression, and increased or maintained ego strength.

The reaction of depletion implies that (1) whether or not treatment would be considered successful, there were other factors, such as disruptive conflict regarding the illness and treatment, environmental problems, other personal difficulties, or an actual loss of a body part, that prevented the patient from conceiving of himself as having renewed strength, with the result that (2)

the elderly person felt that there had been a loss of capacity, either physical or emotional or both, that there had been a continuation of steady or stepwise deterioration, that he or she was less able to carry former responsibilities, less able to meet stress, and that activity must be curtailed, and therefore that (3) the attitude of depletion of one self then acts as a psychodynamic force causing hopelessness, reduced emotional investment outside the self, and withdrawal and increased attention and concern for the self and the body. The remaining ego strength or personal integrative capacity would become more wholly mobilized toward self-preservation and against further disintegration, leaving little for outward expression.

It is proposed that these contrasting reactions of the elderly person to surgical illness and treatment may account for the effects of the hospital experience upon the later course of the aged patient. The effect of "depletion," in our opinion, operates both psychologically and physiologically. The aged patient reacting with "depletion" turns toward emotional rigidity, less activity, more apathy and withdrawal, more depression and projection, more hypochondriasis, and less interpersonal investment. We have hypothesized that the lessened capacity for adapting to stress causes the patient to be more prone to a wide range of physiologic disorders.

The case reported in an earlier section of a woman with a colostomy that could not be closed as she had hoped and with burdensome problems at home is an example of the phenomenon of depletion. She responded to disappointment and a sense of further disintegration with apathy, withdrawal, and depression. She could no longer react with fight and active resistance but became resigned. In our opinion, the cardiovascular decompensation that followed constituted the physiologic side of the reaction to her inarticulate awareness of progressive depletion.

TABLE 3.—*Reactions of Renewal and Depletion*

Renewal		Depletion	
No. cases	11	No. cases	26
Female	3	Female	10
Male	8 *	Male	16 *
Mean age	71.0 †	Mean age	73.9 †
Standard deviation	8.2	Standard deviation	6.8
Information insufficient for evaluation	8		

* Difference in distribution of sexes between reactions is not significant by χ^2 analysis.
† Difference in mean ages between reactions is not significant by *t*-test.

Table 3 presents the statistical findings with respect to renewal or depletion.

The ratio of reactions of depletion to those of renewal in our series was slightly greater than 2:1. The distribution of men and women within the contrasting groups differed but not to the extent of statistical significance. The mean ages of the two groups did not differ significantly, though the patients in the renewal group tended to be younger. The most clear-cut distinction between the groups appeared from inspection of the illnesses presented and the operations performed. In no case among the patients who experienced renewal was there loss of a body part that would curtail activity or function. Some cases in the renewal group faced the possibility of a loss of mobility from a fractured hip. However, each of these patients was saved from being bedfast by the operative insertion of a pin. Three men in the same group had good return of bladder function as a result of transurethral resection of a hypertrophied prostate. Two patients presented tumors which were resected and diagnosed histologically as benign. In contrast, the depleted group included five patients presenting peripheral vascular disease of the lower extremities for amputation. There were five instances of malignant neoplastic disease and two patients admitted as "disposition cases" (a diagnostic category for severely invalided, indigent, and usually aged persons who present the need for chronic hospital care, and who have become wards of the city welfare services). Some of the remainder presented illnesses requiring emergency intraperitoneal surgery. We then have the task of accounting for differences in the reactions of renewal or deple-

tion among the patients with illnesses that are comparable in degree of threat and impairment of function.

Detailed study of the whole protocols of seven cases from the depleted group chosen to match a like number of cases from the renewal group with respect to surgical diagnosis and the hazard and stress of the treatment elicited factors that may distinguish the reactions when the factor of severity of illness or rigor of treatment does not seem sufficient. We found that, in each of the cases presenting depletion, the symptoms of the illness or the part of the body affected, or the surgical procedure imposed either symbolic or actual impairment upon individual techniques for psychological adjustment. The symbolic or actual significance of the body part, the procedure employed, or the illness suffered was vital to the patient's mode of adaptation, and when the body part was removed, or changed, or the illness "cured," there occurred a breach in the psychological defense structure at exactly that point. It appeared as though the special weakness in the patient's resistance to emotional decompensation was found and this crumbling in one area caused weakening elsewhere and, finally, a widespread depletion. It has been noted by Dr. Samuel Newman that the phenomenon of depletion in the aged resembles in many details the psychophysiologic processes that occur in infants experiencing early separation from the mother, as vividly depicted by Dr. René Spitz. These findings with respect to the illness and treatment and the specific underlying emotional difficulty were not demonstrated among the patients responding with renewal.

Table 4 shows the effect among the seven patients manifesting depletion.

The validity of the findings with respect to an explanation for the contrasting reactions of renewal and depletion is limited in two ways. The number of cases studied is small, due partly to the need to match cases from each group with respect to diagnosis, types of surgical treatment, and age. Also, in our opinion, the question of precedence is not wholly resolved. Did the illness itself arouse the organization of defenses around the area involved? This unsettled question does not appear to us to invalidate the findings but raises, instead, an alternate theory, that is, that when it is necessary for a patient to wholly mobilize personality resources around the point of stress, then total adaptation is more brittle and less able to meet further stress.

In summary, we have observed diverse over-all responses to the stress of surgical illness and treatment, the reactions of "renewal" and "depletion," responses that imply attitudes toward the self, with consequent effect upon physiologic function. The factors that separate the two reactions depend upon a complex interaction of personality, physiologic substrate, and the illness and surgery the patient experiences. Two factors are suggested by this research as significant in determining the course: the degree of hazard and severity of the illness and surgery required, and the specific effect of the illness and operation upon the individual defense employed for personality integration.

TABLE 4.—*Examples of Effect of Illness and Surgery upon Individual Defenses*

Case No.	Illness, Symptom, or Surgery	Conflict and Type of Defenses	Effect upon Defenses
63	Cystitis and bladder metaplasia	Abandoned by children; frustrated dependency; hostility *vs.* guilt; reaction formation	Self-disgust, shame, and guilt increased by symptom and treatment, further depression and withdrawal
64	Hemorrhoids and hemorrhoidectomy	"Ungrateful" relatives; patient withdraws and holds emotions in to prevent further loss	Delays treatment; gratification from anal symptom lost; feels punished for anal impulses and powerless
100	Hip fracture pinned	Feeling need for self-sufficiency and independence; denial of passive dependent needs	End of activity with injury means loss of pride and end of life; chronic brain syndrome develops
154	Benign prostatic hypertrophy; transurethral resection	Paranoid in reaction to indifference of relatives	Confirmation of persecutory delusion; surgery final passive surrender; loss of prostate equals loss of vital part of self

Summary and Conclusions

A psychiatric, psychological, and social study of 45 randomly selected and representative surgical patients 65 years and over is reported.

1. Deterioration of mental capacity progressed in 11 cases during their hospital surgical treatment. The following etiologic factors were significant:

(*a*) Patients of 70 and over were more liable to progression of mental deterioration.

(*b*) The acute brain syndrome or delirium preceded chronic deterioration in seven cases.

(*c*) Antecedent anxiety, depression, and severe emotional disturbances were associated with later deterioration in nine patients.

(*d*) Patients who had lost an accepting and comfortable home environment were more liable to deterioration.

2. Depression of a disabling kind appeared in 22 of the total 45 cases. This affect was forced by a complex combination of psychodynamic factors, including perception of lack of capacity to resist everyday stress, hostility and guilt, perception of defect in body image, loss of self-esteem, impairment of ability to remain active, and threat to self-preservation.

3. Projection and paranoid ideation were significant psychopathologic phenomena in nine cases. Principally, this reaction occurred in response to the real or imagined indifference of those persons significant to the elderly patient.

4. Two over-all responses of the aged to surgery are described, the reactions of "renewal" and "depletion." Renewal is intended to characterize a self-concept of repair, hope, and freedom to continue activity and a capacity to invest affect outside the individual. Depletion is intended to characterize an awareness or half-awareness of a sense of personal deterioration, with lessened capacity to meet stress and a need to draw resources inward, to withdraw, and to mobilize for self-preservation. It is theorized that the psychodynamic effect of the reaction of depletion has pathophysiologic consequences.

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Narrowed Attention

A Psychological Phenomenon That Accompanies a Certain Physiological Change

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Introduction

Changes in attention must be reflections of underlying neurophysiological change. While one set of objects or factors occupies the center of attention, more peripheral factors in the environment may still influence behavior. The relative influence of peripheral factors reflects the focus of attention, and a narrowed focus of attention (i. e., a decreased influence of peripheral factors) seems related to some neurophysiological component of acute stress.

The existence of such a relationship can be demonstrated best by uncovering its details, and such details would be most useful. The better one understands how physiological changes influence attention, the better one can predict and control the effects of drugs and emotions. This paper describes a search for details of the relationship between narrowed attention and physiological change.

We first studied the connection between attention and physiological change by observing the way people judge sizes.[1] We had our subjects adjust the size of an object or a projected image located about 200 cm. away so that it would match the size of a similarly shaped object near at hand as nearly as possible. We produced "stress" in our subjects by giving them amyl nitrite to inhale or by having them stick a foot into a bucket of ice water. During such "stress" periods, the subjects tended to make the distant adjustable object larger than they did during "control" periods.

Since our first study, we have confirmed our amyl nitrite observations on a group of 128 additional subjects. On another group, of 20 subjects, we found a strong suggestion that epinephrine (0.01 mg.) and methamphetamine (10 mg.) could produce a similar change in size judgments when compared with control judgments made after injections of saline and arterenol (0.01 mg.).

Although we could not be positive, it seemed that our subjects changed their size judgments because they misjudged distances. Parallax, the shadows and textures of the foreground, relative positions of nearby objects, and many other such cues make distance judgments possible, but such stimuli are somewhat peripheral to the center of attention in the size-judgment experiments. After unsuccessfully attempting to relate our findings to local ophthalmic changes, we came to consider a decreased attentiveness to peripheral-distance cues as the most likely cause of the observed size-judgment change.

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All of the studies reported both in this paper and in the paper that follows were conducted under the guidance and supervision of Dr. Jacob E. Finesinger, Chairman of the Department of Psychiatry. Practically, the experiments were made possible by the technical assistance of Albert Bullis, John Alexander, Jean N. Scher, Charles Parker, and Jeanette Rayner. Many colleagues, both at the University of Maryland and elsewhere, made criticisms and suggestions. Finally, the Maryland Association of Private Practicing Psychiatrists awarded their first annual research prize to some preliminary portions of this work.

Before we could have any real confidence in this hypothesis, a group of alternative theories had to be ruled out. Other explanations for the observed changes in size judgments could be made on the basis of changes in visual accommodation, changes in body image, alterations in the values given to distant or nearby objects, and so on. So many complex things can influence size matching that any demonstration of a size-judgment change must be statistical. The statistical problem of proving the absence of a relatively weak effect became so serious that we were forced to look for other methods. At the end of our experiments on size matching, the data indicated only that the procedures and drugs tried did, in fact, change size judgment.

On the basis of these studies, we formed a working hypothesis. The several methods of producing physiological change all mimic the central component of sympathetic discharge. We hypothesized a common neurophysiological factor and called it "central sympathomimetic activity." When central sympathomimetic activity was increased, our subjects seemed to respond less to things outside the immediate scene. This decreased environmental influence was called "narrowed attention." We then hypothesized a correlation between narrowed attention and central sympathomimetic activity.

To test this idea, we set out to record bits of behavior that would reflect the influence of relatively peripheral factors in the environment. In each experiment, we provoked a neurophysiological change and then measured the dependency of the recorded behavior upon some ordinarily effective stimulus. Increased freedom from peripheral environmental influence was taken to indicate "narrowed attention."

This concept of "narrowed attention" is easily misunderstood. What the general theory means will become clearer as operational details are considered, but before going into our experiments we will try to block a few sources of confusion by emphasizing the following four points.

1. Narrowed attention implies a change in the process which determines how much behavioral influence will be allotted to each possibly influential, relatively current environmental factor. In other words, "narrowed attention" implies something other than a change in the ability to sense a stimulus or to give a response.

2. The more narrowed attention is, the less influence peripheral factors will have on behavior. Here we mean peripheral with respect to time and meaning, as well as with respect to space. In size matching, a subject may direct his attention to distance cues between actual matchings, but, even so, such indications of distance will remain temporally peripheral during actual matching operations. In the second paper of this series, we employ tests where central and peripheral factors overlap in space and time but are separated by differences of meaning. For example, we measure how much printed names of colors interfere with the naming of superimposed conflicting colors.

3. To achieve "narrowing" with respect to external factors, there must be some changes in the influence of internal behavioral determinants. Details must wait on other sorts of experiments, but, from present available data, it would seem that "narrowed attention" augments internal sources of motivation. This does not imply increased rigidity or inability to change set, given some internal motivation for shifting the focus of attention about.

4. Finally, a correlation between "narrowed attention" and increased "central sympathomimetic activity" does not imply any direct causal relationship. Actually, we suspect both changes are secondary to some more basic mechanism—perhaps stimulation of the brain-stem reticular formation.

These four points cover only some of the commonest sources of confusion, but we will turn now to our experiments for further clarification.

Changes in Myographic Activity

One piece of evidence in support of the "narrowed-attention" hypothesis came from

work at the Army Chemical Center.[2] We found that shortly after exposure to one of the nerve gases subjects gave smaller muscle responses to a series of loud sounds. These subjects had been instructed to maintain an even pressure on a rubber ball, and the sudden loud (130 db.) sounds were not at the central focus of these subjects' attention. An increase in electromyographic (EMG) activity recorded from electrodes over the pronator teres muscle served as an indicator of the response to each loud sound. A change in this response following gas exposure was taken to indicate a change in the influence of loud sounds on the particular bit of behavior under study.

The details of the experimental procedure followed closely those published by Malmo et al.,[3] and in scoring our recordings of EMG activity we used their method. For their "myographic index," the electrical activity from 0.4 to 0.6 second following each loud sound is expressed as per cent change from activity during the 0.5 second preceding the sound. Activity itself is estimated by measuring the amplitude of the highest spike in each 0.1-second portion of the intervals considered.

Data from five sound presentations are averaged for each of the myographic indices shown in Figure 1. These results show that gassing decreased the EMG response in all but one case. Of those cases in which readings could be made a day or more after gassing, the myographic index had risen in all but two cases. Statistical tests of these data showed them to be significant at better than the 1% level of confidence.

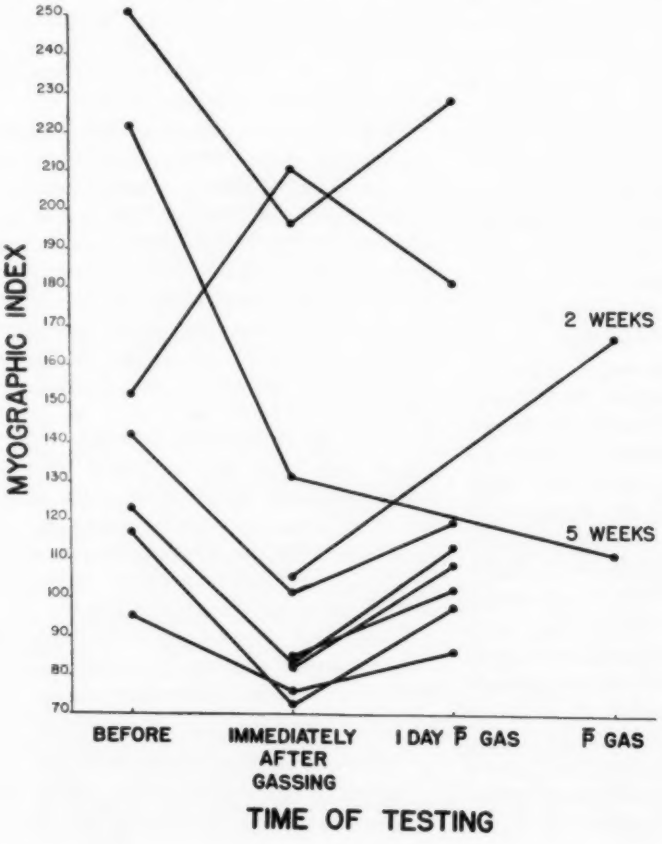

Fig. 1.—Effects of nerve-gas exposure on the myographic index. Each line represents one subject.

The nerve gas, an anticholinesterase similar to isoflurophate U. S. P., causes central sympathomimetic changes on acute exposure. Such anticholinesterases do have striking parasympathomimetic actions on mucous membranes (e. g., myosis and bronchospasm), but, centrally, they affect both the reticular system and the posterior hypothalamus [4-7] and produce a picture like that found when sympathetic activity is increased. Because of these facts, nerve gas can legitimately be said to increase central sympathomimetic activity. On the psychological side, the interpretation is not so simple. The observed decrease in responsiveness could indicate an effect on muscles, an effect on hearing, or, as we believe, narrowed attention; but there is no reason to suspect sensory or motor inhibition, and the variety of experiments to be reported demonstrates the economy of our "narrowed-attention" notion.

If the size-judgment changes and the EMG changes are both manifestations of narrowed attention, a drug that will change size judgments will also change EMG responses. Amyl nitrite seemed the logical drug to use to test this assumption; but since amyl nitrite has less intense physiological effects than nerve gas, we were afraid that any response changes it might cause would be obscured by errors in the manual scoring method.

Davis [8] suggested methods of electronic analysis and scoring; and since such methods promised an appreciable increase in precision, we set out to use electronic analysis in making a new series of observations on the changes in EMG response to sound. The techniques used in these experiments have not been published, and we will give some details of the procedures employed, as well as of the results obtained.

1. *Experimental Procedure.*

(*a*) Subjects: Our subjects were all apparently healthy men and women. They were recruited from the various personnel of the University Hospital and The Johns Hopkins Hospital and were paid for their services. Persons with gross hearing defects or obvious emotional disabilities were rejected.

(*b*) Apparatus: A special integrator circuit was used to record the integral of the EMG. Details of the apparatus may be obtained directly from us. In brief, we picked up the EMG by connecting the grids of a differential preamplifier to the flexor and extensor prominences of the forearm and grounded the wrist of the subject. The EMG was amplified, rectified, and integrated in intervals of 0.22 second each. A two-second tone could be presented so that its onset coincided with the beginning of an integrator interval. The tone itself was of 1000 cps frequency and 110 db. loudness. The room noise was of 50 db. Sound-level measurements were made on a General Radio sound-level meter.

(*c*) Test Procedure: First, a subject was given the following instructions: "This is a device to measure your response to loud sounds. These electrodes will allow us to tell what your muscles are doing. Through these loud-speakers you will hear a very loud sound, loud enough to be unpleasant; however, it will last for only two seconds at a time and won't really hurt you."

The subject was then asked to lie down on a bed, and the electrodes were attached. The subject's arm was positioned so that the forearm was vertical and balanced for a small but definite amount of muscle tension. The EMG was then displayed on a cathode-ray oscilloscope monitor for the subject to see, and this was discussed with the subject to make sure that he understood what was meant by muscle response. He was then told not to make any muscle response to the sounds he would hear. Tones were presented at 40-, 50-, and 60-second intervals in rotation, and the pulse was taken for 15 seconds following each tone.

The first three tones to a subject provoke progressively diminishing muscle responses, but subsequent tone presentations that are spaced 30 seconds to 1 minute apart will provoke more or less consistent responses, and so we disregarded the first three tone presentations in our calculations. The portion of the experimental session that followed these first three "training" tones was broken down into periods. After the three training tones, we presented four tones for a first control period. When this was completed, a drug or placebo was administered and then four more tones were given. This postdrug group of tones was referred to as the test period. Data from a second control period were obtained in some cases, but they were not of sufficient additional value to merit discussion here.

(*d*) Drugs: Just after the first control period, 22 subjects were selected to receive no drugs, and they served as a control group. Twenty-two other subjects received inhalations of amyl nitrite until

a pulse increase of one beat in 15 seconds occurred. Usually considerably more tachycardia resulted, but three subjects were excluded from further consideration because they failed to develop any pulse increase. In addition to these 44 subjects, 7 subjects received 0.005 mg. of arterenol intravenously; 7 subjects received 0.005 mg. of epinephrine intravenously, and 8 subjects received 10 mg. of methamphetamine intravenously.

2. Scoring the Myographic Response.

We defined the EMG response to stimulus as the difference between the EMG just preceding the stimulus and the EMG just following the stimulus. Practically, we computed the average EMG integral obtained during the first 0.88 second of the tone, and then from this value we subtracted the average EMG integral obtained during the 1.1 seconds preceding that same tone. The actual units of our response values are arbitrary, but were consistent throughout the experiment.

According to the above procedure, the data from each subject furnished four response values for the control period and four response values for the postdrug test period (i. e., one response value for each tone presentation). To measure the change produced by a particular substance, we added the four test-period response values together and subtracted this sum from the sum of the four control-period response values. In this way a decrease in response following the test substance yielded a positive value, while the relative increase yielded a negative one.

3. Results.

Table 1 shows the results of this experiment. When no drug is given, the median of EMG response changes is close to zero (actually +0.01). The epinephrine- and arterenol-treated groups do not differ significantly from this control group and, in fact, have a combined median of exactly zero. On the other hand, the amyl nitrite-treated group and the methamphetamine-treated group both differ significantly from the control group by median tests [9] at better than the 5% level of confidence.

These findings are consistent with our theory. The doses of epinephrine and arterenol were too small to have any appreciable affect. On the other hand, the fact that the amyl nitrite-treated group differed from the control group at a significant level of confidence ($\chi^2=4.5$) is even more convincing, because we had predicted the direction of change in advance. In fact, if one accepts the evidence that the median response change is zero when no drug is administered,

TABLE 1.—*Electromyographic Response Changes*

Subject	(Control Group) After No Drug	Repeat Test with Amyl Nitrite	Subject	After Amyl Nitrite	Repeat Test with No Drug
1	28.3	4.9	23	14.6	12.3
2	25.5		24	9.8	
3	19.3		25	8.3	
4	12.2		26	7.0	
5	8.6		27	5.6	
6	5.5		28	5.3	
7	3.2		29	4.5	
8	1.0		30	4.4	
9	0.6	6.7	31	3.5	
10	0.5		32	3.2	
11	0.4		33	2.2	
12	— 0.2		34	1.7	9.6
13	— 0.5	—1.8	35	1.7	
14	— 0.5		36	1.4	
15	— 0.6		37	1.3	5.3
16	— 0.6		38	1.2	
17	— 1.0		39	1.0	
18	— 2.9	9.1	40	0.4	5.2
19	— 3.2		41	— 0.1	
20	— 4.0	0.3	42	— 1.3	— 1.3
21	— 6.0		43	— 2.7	
22	— 7.9	0.8	44	— 7.2	

Subject	After Arterenol, 0.005 Mg.	Subject	After Epinephrine, 0.005 Mg.	Subject	After Methamphetamine, 10 Mg.
45	32.5	52	3.4	59	17.6
46	1.9	53	0.6	60	16.7
47	1.0	54	0.0	61	15.1
48	0.3	55	0.0	62	2.9
49	0.0	56	—0.7	63	2.6
50	— 0.8	57	—2.6	64	1.2
51	— 1.0	58	—3.2	65	1.1
				66	—12.1

one would expect 18 out of 22 responses above zero less than 1 time in 100—if amyl nitrite had no effect. Because of this, we can have some confidence in rejecting a null hypothesis concerning amyl-nitrite modification of EMG responses.

Although the values are statistically significant, the methamphetamine-treated group is small because difficulty in recruiting subjects had become a serious problem. For example, we had hoped to run repeat tests on our first 44 subjects by giving the control subjects amyl nitrite on a second run and by giving the amyl nitrite-treated subjects no drug on their second run. Only 11 out of the first 44 subjects would consent to a second testing. These EMG response changes on second runs are shown beside the subject's first-run values in Table 1. Six of these subjects showed a greater response change on the amyl nitrite test; one showed no difference, and four showed greater response changes after no drug. Although this trend is in the predicted direction, it is not significant.

Summarizing our experience in all of the EMG experiments, we may say that loud intrusive sounds provoke smaller EMG responses after either amyl nitrite or a nerve gas has been given. It is likely that methamphetamine has the same effect, although that series is small.

If these drugs decrease the responsiveness of subjects to things outside the immediate scene, then the intrusive noise would tend to evoke less of a response in subjects that are trying to maintain constant muscle tone. In other words, the nerve-gas and amyl-nitrite data are consistent with the theory that links "narrowing of attention" and "central sympathomimetic activity."

Other interpretations are, of course, possible, and additional data on methamphetamine are needed if one particularly plausible explanation is to be ruled out. Dipping a foot into ice water, being exposed to nerve gas, and inhaling amyl nitrite are all more or less unpleasant. On the other hand, taking methamphetamine is rarely described as unpleasant and is frequently enjoyed. Other evidence would suggest that a subject finds it more unpleasant to wait for an injection than to experience the effects of methamphetamine. Because of these facts, the demonstration of "narrowed attention" following the injection of methamphetamine would allow us to show that "narrowed attention" is not simply a side-effect of an unpleasant situation.

Galvanic Skin Response Experiments

The galvanic skin response, or GSR,[10-12] is very sensitive to external stimuli. Measurable changes may be produced in a person's skin resistance by setting off a flash bulb, by blowing a horn, or by having the person give out loud his associations to stimulus words. By adopting the GSR as an indicator of response, we dispensed with the unpleasant 110-db. sound that was required for the myographic studies but continued our investigation of methamphetamine as an agent for producing narrowed attention.

A. GSR Experiment I

1. *Experimental Technique.*

(*a*) Subjects: Twelve University of Maryland medical students were paid to take part in these experiments.

(*b*) Apparatus: The apparatus was adapted from that described by Flanders.[13] The skin resistance was determined by applying a constant current across two solder electrodes fixed to the palm of the subject's hand with adhesive tape and electrode jelly. The voltage developed was fed into a Sanborn recorder. A measured potential was used to cancel out most of the base-line potential so that small resistance changes could be more easily measured. Voltage was expressed as resistance because, with a constant current, voltage is proportionate to resistance. The subject was seated in a shielded room, and recordings were made from a soundproof room adjoining it. The operator could observe the subject through a one-way mirror.

(*c*) Test Procedure: Subjects were told that they would receive two tests and that during one test they would be given 0.5 cc. of saline intravenously, while during the other they would receive 10 mg. of methamphetamine hydrochloride intravenously. The order of these substances was

unknown to the subjects. The tests were separated in time by at least a week, and each test followed the same form. The subject was first seated in a soundproof room with subdued lighting. He was told that the electrodes were to measure his skin resistance, and after the electrodes were in place, he was given a brief, but accurate, description of the schedule for the various procedures. This schedule was as follows: 1. The subject was instructed to relax, but not to sleep (subject alone for 20 minutes). 2. The technician entered the room. 3. Eighteen words were given for timed association, one each 15 seconds over a loudspeaker. The subject was instructed to give verbal responses as rapidly as possible and was told that a technician would time his responses with a stop watch. 4. Other stimuli were then administered at one-minute intervals. These were (*a*) a horn, (*b*) a flash bulb, (*c*) a smell of vanilla or almond extract, (*d*) dipping the hand into ice water, and (*e*) gripping an object. 5. The overhead lights were then turned on, and the subject was given a book to read alone for five minutes. 6. At this point the examiner entered the room and gave an injection. 7. Steps (1) through (5) were then repeated.

The probable effectiveness of various words in producing galvanic skin responses has been determined.[14] From these data we constructed three word lists that were designed to elicit comparable average GSR's. Word list 1 was always used on control runs; word lists 2 and 3 were used on the first and second postinjection runs, respectively. Our data showed that the effectiveness of the lists was comparable, but since half of our group received saline before their first postinjection run, with the other half receiving methamphetamine first, any differing effects of the word lists were apportioned out in the final results.

(*d*) Scoring: The record was calibrated so that the skin resistance at any time could be expressed in ohms. After each stimulus a sharp drop generally occurred. The peak resistance just before that drop and the minimum resistance occurring immediately after the stimuli were both written down as ohms. The average basal resistance was calculated directly from these values. Following the work of Lacey and Siegel,[15] the change caused by the stimulus was computed in conductance units (mhos) rather than in resistance units (ohms). To obtain these values, both peak and trough values were converted from ohms to micromhos by taking the reciprocal and multiplying by 10^6. The difference between these values was expressed as a change of so many micromhos.

2. *Results.*

In calculating the results of this experiment, we discovered a small variable error, which was due to a defect in our calibrating system. There was no reason to assume that it could, in any way, account for the significant changes produced by methamphetamine, but the second experiment was conducted with an improved machine, and the data from this first experiment should be considered in the light of this possible error. Examination of the data from the first experiment revealed the following findings:

1. For control (preinjection) runs, the mean response, in micromhos, for the word associations showed a test-retest correlation of +0.86.

2. Basal resistance tended to fall after injections, and this occurred whether the injections contained saline or methamphetamine. The decrease in basal resistance was greater following methamphetamine in most cases, but this was not statistically significant.

3. After saline, conductance changes were usually larger than during the control period, while after methamphetamine they were smaller than the control. Taking individual responses, saline, methamphetamine, and control responses all differed from each other at better than the 1% level of confidence by the χ^2 test.

4. The responses to smelling, to gripping, and to putting the hand in ice water were difficult to evaluate, since the preparations for these procedures usually caused more change in conductance than the procedures themselves.

B. GSR Experiment II

1. *Experimental Technique.*

(*a*) Subjects: Six subjects were all paid volunteers recruited from the nursing and psychiatric aide personnel of the Psychiatric Institute.

(*b*) Apparatus: The apparatus was similar to that used in the first experiment; however, instead of relying on a measured voltage to cancel out large base-line variations, a series of precision resistors and an identical balanced constant-current generator supplied such a "bucking" voltage. Resistance-change calibration was accomplished by switching a precision resistor in series with the subject. Careful checking revealed this device to

have an error of approximately 1% in measuring basal resistance, and it allowed the measurement of changes on the order of 0.1 micromho. Another change in technique involved the substitution of calcium chloride and bentonite paste for the electrode jelly which was used in the first experiment. This paste tended to dry out less in these prolonged experiments than did the electrode jelly and could be fixed to the hand with adhesive tape more easily.

(*c*) Procedure: The procedure was as before except that the relaxation period was dropped to 15 minutes and only light and sound were used as nonverbal stimuli. The same three word lists were used as before, and, as before, word list 1 was always used as a control. Thus, the subject received it twice. The other two lists were used after the injections and were administered as before so that each was given to the same number of subjects with methamphetamine as with saline.

(*d*) Scoring: This was done as in Experiment I.

2. *Results.*

We observed the same over-all pattern of results as before, but there were some differences. This time the individual word-association GSR's with methamphetamine differed from both the control and the saline responses at better than a 1% level of confidence by χ^2, but, as opposed to the first experiment, the saline responses did not differ significantly from the control ones. The correlation coefficient for control (i. e., preinjection) GSR's obtained at the first experimental session and those obtained at the second was lower in this experiment than in the first experiment ($R = +0.39$, as opposed to $R = +0.85$). The slight tendency for methamphetamine to produce a greater drop in skin resistance than did saline which was found in the first experiment was not encountered at all in the second experiment.

C. Summary of GSR Results

In Table 2, we have compressed our raw data on these galvanic skin response experiments by averaging the differences between the pre- and postinjection values. Postinjection increases are positive; decreases are negative. Average changes in basal resistance, average changes in galvanic skin resistance to words for association, and average changes in galvanic skin resistance to the nonverbal stimuli (i. e., horn and flash) are given for each subject on both saline and methamphetamine runs. Such a condensation obscures some differences that can be demonstrated with the raw data, but the over-all results are still apparent and statistically significant. In four subjects

TABLE 2.—*Changes in Basal Resistance and Galvanic Skin Response After Injections*

Subject	Change with Saline			Change with Methamphetamine		
	Average Change in Basal Resistance, in K Ohms	Average GSR Change, Micromhos		Average Change in Basal Resistance, in K Ohms	Average GSR Change, Micromhos	
		To Words	To Flash and Horn		To Words	To Flash and Horn
			First Experiment			
1	0	+1.0	+0.5	0	−4.5	−0.7
2	+2	+0.5	−3.8	−9.0	−0.3	−1.9
3	+4	+1.4	−1.3	−5.0	+1.2	−1.1
4	−2	+1.0	−1.4	−2.0	+1.7	+0.4
5	0	−0.6	+0.1	−11.0	−1.2	−2.2
6	−2	+0.8	+2.7	−2.0	−1.2	−1.8
7	0	−0.1	−1.6	−4.0	−2.1	−4.4
8	−4	+1.0	+2.9	−4.0	−0.2	−0.5
9	−2	+2.4	+2.6	−10.0	−0.4	−2.5
10	−2	+3.6	+2.4	−9.0	+0.1	+0.4
11	−2	−0.3	−0.8	..	..	−4.0
12	−6	+1.1	+1.3	−1.0	−0.2	+0.9
			Second Experiment			
1	−12.1	+1.78	+1.6	+2.4	−0.55	−1.5
2	−4.0	+0.49	−3.9	−9.8	−0.61	−6.7
3	−10.1	+0.31	+3.9	+4.6	+0.23	+6.0
4	−14.3	+0.45	−0.6	+8.2	−0.41	−4.1
5	−2.6	+0.30	−1.3	0	−0.38	−1.1
6	−5.0	−1.32	−2.3	−0.9	−1.31	−6.0
Saline change > methamphetamine change				7	15	13
Changes equal				4	0	0
Methamphetamine change > saline change				6	2	5
P value of above changes					0.002	0.04

there was no difference between the basal skin resistance changes on methamphetamine tests and those on saline tests. The other 12 subjects were evenly divided, with 6 showing more of a decrease after methamphetamine, and 6 showing less of a decrease. Certainly, methamphetamine seems to have no consistent effect on basal skin resistance.

This is not true of the changes in galvanic skin responses. We predicted that there would be more of a decrease in these responses following methamphetamine than following saline. This occurred in 15 out of the 17 subjects in the word association responses. This would be expected by chance about 2 times in 1000. Responses to the nonverbal stimuli were relatively smaller after methamphetamine—13 out of 18 times. This would occur by chance about 5 times in 100. Thus, even from summarized data it is apparent that methamphetamine did not significantly affect basal skin resistance but did decrease response both to word associations and to horn and flash stimuli.

The galvanic skin response experiments using horn and flash stimuli are analogous to the myogram experiments. The horn and flash are intrusive stimuli. After methamphetamine our subjects responded less to such stimuli, regardless of whether the response measured was an EMG response or a galvanic skin response. By assuming that methamphetamine produced a narrowing of attention, we can explain the results of both these experiments with a single theory. While alternative explanations still remain, the GSR experiments do exclude one theory that is possible on the basis of the EMG data alone. We used the phrase "narrowed attention" to imply something other than a change in the ability to perform a response. We had no way to be sure that the EMG changes did not reflect some impairment of peripheral neuromuscular functions. We can, however, discard such an explanation for the GRS results. If something inhibits the peripheral sympathetic-sudomotor complex, there will be a change in average or base-line skin resistance. This was not observed after methamphetamine, and therefore we must assume that the decrease in GSR after methamphetamine indicated some change in a function that precedes the peripheral sympathetic discharge. In summary, then, a decrease in galvanic skin responses could indicate (1) impaired sudomotor functioning (e. g., as after atropine) or (2) central changes in responding to stimuli. The effects of methamphetamine on flash and horn galvanic skin responses could not be explained on the basis of sudomotor impairment because there were no basal skin resistance changes; and since subjects could not have the unpredictable and brief light or sound stimuli at the center of attention, decreased responses to these peripheral stimuli were taken to indicate narrowed attention.

A more involved explanation is demanded for the decreased word-association GSR's. Usually the stimulus word and the response occupy the center of the subject's attention. However, if the subject thinks of an association without verbalizing it, little or no galvanic skin response occurs, and so neither the centrally attended stimulus word nor the association word is a chief stimulus for the GSR. Instead, the GSR would appear to reflect attention to those peripheral factors that must be observed in keeping any verbal response socially acceptable. Awareness of the female technician who was recording times, and of a staff physician who was listening over the sound system, all contributed to the "alerting" required with each association given out loud, and it would seem that methamphetamine reduced responsiveness to such "peripheral factors." Clinically, we would suspect that the well-known uninhibited speech and action of methamphetamine-treated subjects are additional evidence that the drug makes people less broadly attentive to how the environment is receiving their productions.

The Guessing Game

Up to this point, we had measured behavior that reflected peripheral environmental influence, but each experiment had

also been sensitive to changes in sensory or motor functioning. Since the "guessing-game experiment" [16-18] is unaffected by wide swings in sensory or motor ability, we felt it would be appropriate as a final experiment.

The procedure consists of having a subject guess which of two events will occur and then observe whether the guess was correct by watching an event. After each event observation, a new guess is made, and so on, over and over again. If the two possible events occur with equal frequency, subjects will guess for these events with nearly equal frequency. However, when the relative frequency of one event decreases, subjects will slowly decrease the frequency of guessing for that event, and the frequency of guesses for given events will approach the actual frequency of the events asymptotically. In such an experiment, if the subject is capable of writing down his predictions about the next event, his behavior will be independent of any changes in ability to respond, while the observed events can be made so gross that subtle sensory changes become unimportant.

We use "narrowed attention" to indicate a decrease in the influence of peripheral factors, and we have defined peripheral factors as "those relatively current environmental events which are removed from the central focus of attention by space, by time, or by differences of meaning." In the guessing game the central focus of attention will be held alternately by the current guess and the current answer, while at the same time past answers will be temporally peripheral. Characteristics of past sequences, lengths of run, or some other functions of past answers are influencing behavior when guess frequency changes in response to changed-answer frequency.[19] Since past answers are continually peripheral to current guesses, guess-frequency response to answer-frequency change reflects the influence of peripheral factors upon behavior. In other words, it can be used to indicate narrowed attention. In specific terms, we predicted that methamphetamine would produce narrowing of attention, and therefore methamphetamine-treated subjects would respond to a changed-answer frequency more slowly than would control subjects.

1. *Experimental Technique.*

(*a*) Subjects: The subjects consisted of 20 paid volunteer first-year medical students at the University of Maryland.

(*b*) Apparatus: The apparatus consisted of two small light bulbs mounted about 4 ft. apart on a strip of white cardboard. One light bulb was labeled "a" and the other "b." They were fed through a three-position switch so that "a" could be turned on, both lights could be turned off, or "b" could be turned on.

(*c*) Experimental Procedure: The experiment consisted of two tests one week apart. On the morning of each test, envelopes containing two pills, a sheet of instructions, and a series of small booklets were given out. The subjects were also told that one morning the two pills would contain 5 mg. of methamphetamine each, while on the other morning they would be sodium bicarbonate tablets. Each booklet was to be signed and labeled "A" through "H." The pages in each booklet were numbered 1 through 20. At 10:00 a. m. the subjects took the pills, and at noon the test was conducted. The subjects were told that the experiment itself would consist of making a number of guesses as to which of a pair of lights would come on. Questions as to the nature and meaning of this experiment were deferred until the completion of the test. In the actual tests, the subjects were scattered about in a classroom. Instructions were reviewed, and the lights were demonstrated. Then the following sequence of instructions accompanied the presentation of the lights at 10-second intervals. 1. Booklet A, Page 1: "Make your guess." 2. "Guesses made? Then turn the page." 3. "This is the light." 4. Booklet A, Page 2: "Make your guess," etc. The first 20 lights in each test (Group A) were evenly divided between light "a" and light "b." In the other seven series of 20 lights (Groups B through H) one light was turned on 16 times and the other light turned on only 4 times. During the first test the most probable light was light "a," and the next week it was light "b." The actual sequences were selected from tables of random numbers, with the following restrictions: (1) No more than two unlikely lights in succession were allowed, and (2) the specified frequency occurred in each group of 20 lights. The subjects had been divided into two groups of 10 each. On the first day one group received methamphetamine pills, and the other got soda tablets. On the test the following week the groups were reversed.

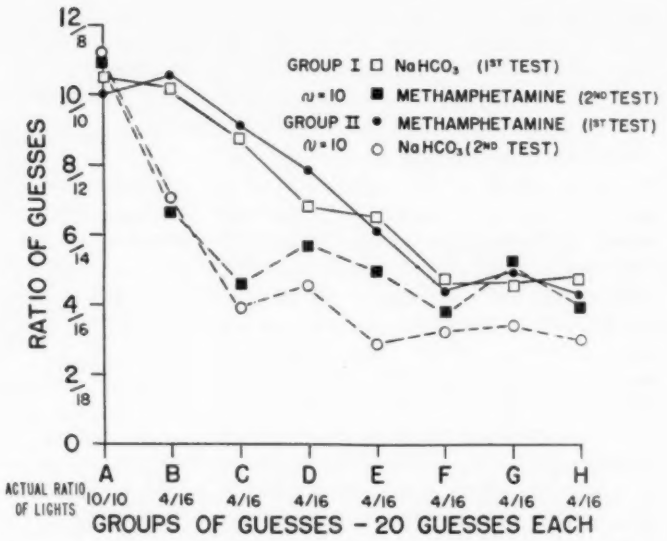

Fig. 2.—Effect of methamphetamine on guess frequency.

2. *Results.*

Figures 2 and 3 show the results of this experiment. In Figure 2 the actual frequency of guesses is shown for each of the two groups separately in each of the two tests. As would be expected, there was a strong tendency to shift guesses more rapidly the second time through, but each time the group receiving methamphetamine changed more slowly than the sodium bicarbonate-treated group.

From Figure 2, it seems that at least two observable factors influence the number of guesses a subject will make for the unlikely light. These two factors are (1) his past experience with the test, and (2) the effects of the drug. By subtracting "unlikely light guesses" on the first test from the same score on the second test, we equalize the experience factor in the two groups. Any remaining difference between the two groups may then be attributed to the drug. We predicted that those who received methamphetamine would be less influenced in their guessing when one of the lights became relatively unlikely. Because of this, they

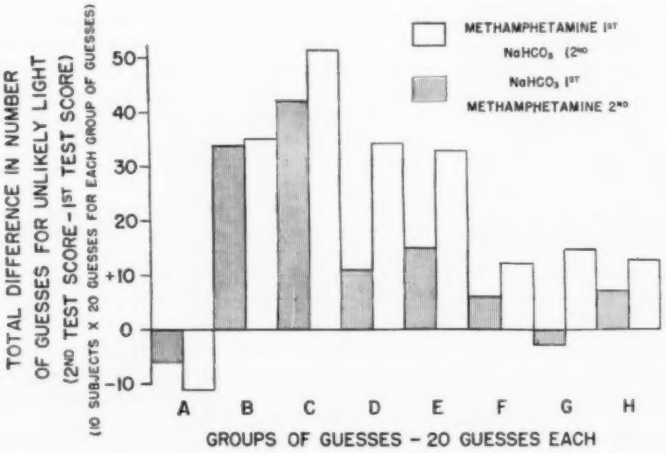

Fig. 3.—Change in number of guesses for the "unlikely light" from first to second test as influenced by methamphetamine.

would make more "unlikely light guesses." If a subject received methamphetamine on the first test, he would show a greater drop in "unlikely light guesses" the second time through than would a subject under drug influence on the second test. Figure 3 shows that this is the case. Statistically, the means of such difference scores for the two groups differ by the *t*-test at better than the 5% level of confidence.

Comment

Some physiological counterpart of sudden and strong emotion increases the selectivity of one's attention. People become "numb with fear" and "blind with rage." The football player ignores his broken hand until the whistle blows; the disaster victim remembers small incidents in great detail but gives a vague and distorted description of the broader picture. Kinsey [20] describes how orgasm narrows attention, so that broken ribs and lifted wallets go unnoticed. Laboratory demonstrations supplement such anecdotal material. Shipman [21] found that when children are waiting to see the dentist, they recall fewer details of their surroundings than do suitable controls. She says: "Thus, the constricting effect of stress was shown to be generalized to various perceptual behavior . . . and . . . the subject under stress is not as aware of as many cues in his environment." Kohn [22] studied the recall of details from pictures and stories under varying degrees of induced stress. He concludes: "Severe emotional stress reduces the scope of complex perceptual activity." And he adds "the efficiency of observation is decreased more for irrelevant than for relevant items."

In our studies, drugs were used to produce narrowed attention, and behavioral changes were measured by a variety of methods. Changes in size judgment were used to reflect increased freedom from the effect of distance cues. The myogram and galvanic skin response indicated sensitivity to peripheral environmental stimuli in a straightforward way, while the guessing game supplied us with a subtler measure. Strategies of predictive behavior are based on an extended awareness of temporally peripheral past stimuli. Our methamphetamine-treated subjects were less able to utilize characteristics of extended sequences in formulating their predictions. In general, then, if an environmental situation influences behavior without occupying the center of the subject's attention, a decrease in the influence of such an environmental situation indicates narrowing of attention.

By using drugs instead of emotions to narrow attention, we can come closer to specifying the essential physiological correlate. First of all, we can rule out the possibility that narrowed attention is a result of some affect, such as fear or anxiety. For illustration, one may compare the affects likely to be produced by exposure to nerve gas or by immersing a foot in crushed ice with the affects experienced by medical students on taking methamphetamine by mouth. Looking for some common denominator, we first noticed that every drug that caused narrowed attention could be classed as a "central sympathomimetic." On closer inspection, we found they all evoke an "alert" EEG, presumably by stimulating the brainstem reticular formation, and they have this action in common with fear, strong excitement, and orgasm. In other respects, the drugs and emotions that narrow attention seem to have little in common.

Some of the physiological evidence for grouping these drugs and emotions together as sympathomimetic activating agents was presented in an earlier publication,[23] and much of the more recent physiological data has been carefully covered in a paper by Bradley and Elkes.[24] In this paper they also take pains to point out the dissociation of behavior and electroencephalographic activity induced by the anticholinesterases and atropine. For instance, amphetamine produces both behavioral and EEG arousal. Physostigmine, on the other hand, induces EEG arousal without behavioral arousal. Amphetamine is similar to methamphetamine,

and physostigmine is similar to the nerve gas. Amyl nitrite produces reticular-system stimulation pharmacologically,[25] and it may also be considered something of a noxious stimulus.

In speculating about the sorts of receptors in the central nervous system that might be responsible for the effects of anticholinesterases and atropine, Bradley and Elkes say: "One is almost certainly cholinergic in nature, and its activation or blockade leads to effects on electrical activity which in the conscious animal are not necessarily related to behavior." From our studies, it would seem that narrowing of attention may be the missing behavioral correlate, and studies on the psychopharmacology of atropine would be most interesting in light of this possibility.

Neurophysiological evidence supports the notion that certain changes in the reticular formation may be related to changes in the focus of attention. Stimulation of the reticular formation directly and indirectly may inhibit conduction of impulses up the long spinal afferent pathway [26] and may also prevent the "thalamic recruiting response." [27,28] The neurohumoral results of reticular-formation stimulation may be inhibitory,[29] and Marrazzi [4] had emphasized the inhibitory action of epinephrine in the central nervous system. The relationship between drugs and the ability of the reticular formation to modulate activity in sensory afferent systems has been emphasized by Killam and Killam,[30] and they suggest that certain drugs control the "filtering effects of the reticular formation on lateral sensory pathways with little effect on the reticular mechanisms of consciousness." Here the term "filtering" implies a selective reduction of input, as opposed to an indiscriminate inhibition. Finally, Evarts and Magoun write:

> The effects of brain-stem stimulation have customarily been given blanket equation with awakening, but depending on the state of the animal and the parameters and location of stimulation, such stimulation would appear to be capable of leading to a wide spectrum of behavioral changes that range from awakening to the evocation of attention, to startle, or to the arousal of generalized excitement.[31]

Along with cortical arousal and sensory filtering, the reticular system probably also influences motor readiness. It is often difficult to separate motor and sensory effects in observations of behavioral end-results, and this is a potential source of confusion in interpreting experimental results. Sometimes the distinction between increased motor readiness and decreased peripheral sensory responsiveness is easy to make. For instance, Schaefer et al.[32] found that carbon dioxide increased the myographic activity in resting subjects but decreased myographic responses to sudden, unexpected stimuli. This directly parallels our own myographic observations on methamphetamine and amyl nitrite, since Gellhorn [33] has shown that carbon dioxide is a central sympathomimetic.

The distinction becomes less clear in some of the conditioning experiments done in studying Hullian drive theory.[34] With simple eyelid conditioning, high anxiety levels lead to more rapid conditioning, but if the conditioning situation is a more complex one, high anxiety causes inferior performance. Classical Hullian theory postulates that anxiety and drive level are related. Drive level is thought to operate on all of the habits activated in a given situation and to bring them all nearer to the threshold for action. When a particular situation evokes a single response, high drive level leads to superior performance, but when a variety of competing responses are aroused, a high drive level potentiates incorrect, as well as correct, responses and performance deteriorates. In other words, this theory relates the entire set of findings to changes in motor readiness. Nevertheless, in some experiments designed to demonstrate the adverse effects of anxiety on performance, the situation not only evokes complex responses but also demands the use of a wide field of attention. It is very possible that the results in some of the Hullian experiments reflect a narrowing of attention, as well as the activation of competing responses.

This difficulty of distinguishing between motor and sensory effects can also be illus-

trated by some studies on impulsive behavior. Laufer, Denhoff, and Solomons[35] describe hyperkinetic children as being "unusually sensitive to stimuli flooding in from both peripheral receptors and viscera." In such cases, they found that amphetamine improves the children clinically, raises their abnormally low photo-Metrazol thresholds, and probably serves to "alter the functions of the diencephalon in such a way that it once more can keep the cortex from being flooded." This would fit with our "sensory" theories and with our experimental observations on methamphetamine. The complementary "motor" explanation has been well presented by the Laceys.[36] Of this work on hyperkinetic children, they write: "Their results are congruent obviously with our theory: Easily aroused diencephalic-cortical mechanisms produce higher levels of cortical activity, leading to motor facilitation and augmentation." This statement was made on the basis of a series of excellent studies that relate impulsive behavior to the rate of spontaneous aperiodic autonomic fluctuation. The Laceys find that reticular-system stimulation, spontaneous autonomic activity, impulsivity, and motor readiness are all apparently related. For instance, in one of their experiments, the Laceys measured reaction times to centrally placed visual stimuli. To either side of this central stimulus, and subtending various angles with the central point of fixation, occasional extraneous stimuli were presented, and these peripheral stimuli were to be ignored by the subject. Among other things, these workers measured the frequency of erroneous impulsive motor responses to these peripherally placed stimuli. They found that subjects with a high frequence of spontaneous autonomic fluctuation—the so-called autonomic labiles—made more erroneous impulsive responses than did the autonomic stabiles.

Some of our own data would support the interpretation given by the Laceys to the Laufer, Denhoff, and Solomons experiment. Looking back over the GSR records obtained in our methamphetamine experiments, we found that methamphetamine apparently decreases the rate of spontaneous autonomic fluctuations. Thus, amphetamine improves the behavior of hyperkinetic children; spontaneous autonomic fluctuation is related to hyperkinetic and impulsive behavior, and methamphetamine—pharmacologically very similar to amphetamine—decreases spontaneous autonomic fluctuations in the GSR. At the same time, there is evidence in the published work of the Laceys to support our "sensory" interpretation of the Laufer, Denhoff, and Solomons experiments. The larger the angles subtended by the peripheral visual stimuli in the Laceys' experiment, the less frequent were impulsive erroneous responses. The rate at which the frequency of erroneous responses decreases as the visual angle increases is known as the "gradient," and the Laceys predicted that "impulsivity . . . should be associated with 'flat' gradients, in which the peripherality of the light does not have a sharp effect on the ratio of the frequency of false responses to a given light, on one hand, to the total frequency of false responses to all lights, on the other." This, however, is not what the Laceys observed, and they write: "If anything, the gradients are steeper for labiles than for stabiles when the percentage of false responses is plotted, implying greater sensory discrimination among light positions by the labiles." The situation is obviously a puzzling one. At this point, it would seem likely that autonomic lability, autonomic tonus, motor readiness, and sensory filtering are all somehow related, but just how and to what degree remains to be determined.

Perhaps the most difficult problem of all is that of determining the relationship between attention and internal processes. We have viewed attention as a kind of central gaiting or filtering that makes selections among peripheral external determinates of behavior, and we have tried to make our experiments insensitive to internal factors, such as habits, genetic potential, expectations, and older memories. This has been

done largely by the device of using the subject as his own control. Nevertheless, it is absurd to consider stimuli from the environment as existing in an isolated instant of time, and so even the external determinates of behavior at a given moment are composed of memories as well as sensory stimuli. Finally, increased selectivity with respect to sensory data may imply increased reliance on internal factors, but this important implication has received no attention in these studies.

Even with our ignorance of the influence of internal factors, and of the relationship between focus of attention and motor readiness; our concept of narrowed attention as a kind of peripheral sensory selectivity is useful, and its utility can be illustrated by clinical observations made on methamphetamine-treated subjects. We will give two examples, one in which the subject enjoyed the effects of the drug, another in which the subject disliked the effects of the drug; but in both situations the effects illustrate narrowing of attention.

As an example of "pleasant" narrowed attention, we could mention the student who had a broken arm. His arm was in a cast during the experiments, and after the injection of methamphetamine he described how he was better able to ignore the nagging discomfort of his immobilized arm. "Unpleasant" narrowed attention can be illustrated by the example of the shy young medical student who became extremely talkative after his injection. He spent some time trying to make a date with the technician, who, in turn, tried to communicate her lack of interest by various polite and subtle techniques. The student was so oblivious to these peripheral cues that the technician finally brought her communications to the center of attention by saying point-blank, "I do not want to go out with you." Later the student described how this episode turned his euphoria to depression. He spent much of the rest of the day thinking how he had made a fool of himself, and peripheral factors, such as television, studies, and the conversation of his colleagues, all proved ineffective in distracting him from his depressive ruminations.

Although a number of other "clinical" illustrations could be given, the really important details of the relationship between the focus of attention and clinical pathology remain to be studied.

Conclusions

Narrowed attention is inferred when the behavioral influence of peripheral factors diminishes. Reported experiments include (1) changes in size matching produced by amyl nitrite, by epinephrine, and by methamphetamine; (2) changes in muscle response to loud sounds produced by nerve gases, amyl nitrite, and methamphetamine; (3) changes in galvanic skin response produced by methamphetamine, and (4) changes in guessing behavior produced by methamphetamine. All of the observed changes indicated narrowed attention. We have reviewed the literature and find evidence that both emotional states, such as anxiety, panic, and orgasm, and chemical agents, such as amphetamine and carbon dioxide, produce a similar narrowing of attention. The evidence is analyzed, and a correlation between narrowed attention and central sympathomimetic activity is demonstrated. Stimulation of the reticular activating system may inhibit sensory function, and reticular-system stimulation is considered the part of central sympathomimetic activation that is linked most directly to narrowed attention. Problems with this concept and some clinical implications are briefly discussed.

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Correction

On page 512 of the November, 1957, issue of the ARCHIVES, the two paragraphs of small type beginning on the third line of the left-hand column are a continuation of the footnote at the bottom of the column and not part of the original text of Professor Delay.

Some Psychopharmacological Effects of Atropine

Preliminary Investigation of Broadened Attention

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Introduction

On the basis of data in the preceding paper,[1] we suspect that the focus of attention is influenced by changes in the brain-stem reticular system. Drugs and procedures which produce electroencephalographic arousal also produce narrowing of attention; and this relationship between EEG arousal and narrowed attention holds even for anticholinesterases, although these compounds may produce an aroused EEG without apparent behavioral arousal.

According to our theory, any drug that produces the opposite of EEG "arousal" (i. e., EEG "drowsiness") should also produce the opposite of "narrowed attention" (i. e., "broadened attention"). Theoretically, "broadened attention" might be produced by morphine, pentobarbital (Nembutal), or atropine, since all three drugs (1) induce high-amplitude slow-wave activity in the EEG (i. e., a drowsy record); (2) raise the threshold for EEG "arousal" from reticular-formation stimulation, and (3) block pituitary activation in the proestrus rat.[2] Pentobarbital and morphine produce sedation, and actual drowsiness might obscure changes in the focus of attention. Atropine, on the other hand, seems to operate at the same site as the anticholinesterases and produces EEG-behavioral dissociation. For example, animals treated with atropine may act alert in spite of drowsy EEG's.[3-8] Other workers refer to atropine as a cortical stimulant.[9] For our purposes, then, atropine is an ideal drug to use in continuing to study the focus of attention. At the same time, such a study on atropine would be compatible with two additional goals. First, some correlations between drug reactions and personality reported by Kornetsky and Humphries[10] seemed worth trying to reproduce. These workers reported correlations between objective drug-induced changes, subjective drug response, and factors measured by the Minnesota Multiphasic Personality Inventory (MMPI). Second, we had some general curiosity about the clinical psychopharmacology of atropine. As the best-known acetylcholine-blocking agent, this drug has many characteristics common to certain of the new ataractic agents, but it has not been well studied psychopharmacologically.

Primary Experimental Procedure

I. Subjects.—Our subjects were 21 first- and second-year medical student volunteers, who were paid for their service.

II. Basic Work-Up.—Each subject received a basic work-up, which consisted of an interview of at least one hour with a psychiatrist, the Minnesota Multiphasic Personality Inventory, and a pretest on the Stroop Color Naming Test. All subjects completed a preliminary Stroop test and the MMPI prior to the first drug experiment, and the interviews were completed later on, when the time was available. A majority of our subjects also were given Rorschach tests.

III. Method of Studying Drug Reactions.—Ten of our subjects received 2 mg. of atropine sulfate intramuscularly in 1 cc. of water during their first drug experiment and 1 cc. of saline intramuscularly during their second. Eleven other subjects received the same injection in reverse order. Drug experiments were spaced at least two weeks apart, and in most cases a month apart. On the day of each drug experiment the subjects

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reported to the laboratory and received an injection. After a 15-minute wait, they went through a battery of test procedures which were designed to measure both objective and subjective changes.

IV. Objective Test Procedures.—We used four different objective test procedures which have been reported in the literature. In addition, we tried out two new tests of our own design, which proved unsatisfactory on technical grounds.

A. The Stroop Test[11]: This test has been described in detail by Thurstone[12] and used more recently by Klein and his group.[13,14] The subject is first shown a card on which the words RED, GREEN, YELLOW, and BLUE are printed a number of times in random order, and he is instructed to read these words as rapidly as possible. After this he is given a second sheet, on which a number of spots have been tinted with the four primary colors. He is instructed to name these colors as rapidly as possible, and the time required for naming these colors is recorded. A third sheet contains the primary colors superimposed on the printed names of colors, but in each case the actual color is superimposed on a conflicting name. For example, the printed word GREEN might be tinted red, yellow, or blue, etc. The subject is told to ignore the printed words and to name the actual colors as rapidly as possible. The time taken in reading colors from this card is recorded. The score on the Stroop test is obtained by taking the arithmetic difference between the time for colors alone and the time for colors-on-words. This score represents the increased time needed for naming colors when this performance is being interfered with by printed words. All of our subjects were given one Stroop test at least two weeks prior to the beginning of the first drug run because a preliminary study showed that learning influences scores obtained on this test. Experience is to some extent adapted out if tests are placed at least a month apart and if one preliminary test is disregarded, to accommodate the steepest portion of the learning curve. Stroop, Thurstone, and Klein used the ratio between the two times, but in pilot studies we found that such a ratio did not give as good test-retest correlations as did the simple difference.

B. The Gottschaldt Test: The Gottschaldt test has also been described in detail by Thurstone, while Klein and his associates found it to correlate with the Stroop test. In this test the subject is shown a simple figure and then asked to find it hidden within a more complex figure. To solve the problem, the subject must destroy a given gestalt to form a new one. There are two groups of such figures, known as the Gottschaldt A and the Gottschaldt B. Although the two tests are not exactly comparable, they correlate well with each other. The number of correct answers and the time required for the solutions are both used in scoring.

C. The Progressive Matrices (Sets A through E, published by Western Psychological Service): This is an intelligence test designed by Raven.[15] The subject selects one of a series of smaller figures that he feels would complete a larger pattern. These larger patterns, or matrices, progress in complexity. The subject is instructed to work accurately since speed is only of secondary importance. We split this test into two parts by taking alternate problems from the easiest to the most difficult. In this way we made two roughly comparable and highly correlated test procedures. As with the Gottschaldt tests, we recorded the number of problems correctly solved and the time required to complete the test.

D. The Luchins *Einstellung* Test: This test is also known at the water-jar test. It has been widely used to measure "rigidity"; but this use has been critically reviewed recently by Levitt,[16] and our use of this test does not imply that the focus of attention and rigidity are necessarily related. The test consists of a series of 10 arithmetic problems. In each problem the subject must figure out how to obtain a given volume if he has vessels of three different capacities. The first four of these problems can be solved in only one particular way. The next four problems can be solved in either the same way as the first four or by a simpler, new method. The last two problems cannot be solved at all by the older method and can be solved only by the new method. Following Pally,[17] we scored the test in terms of time required for the subject to solve a problem by the short method or to complete the entire test if he failed to adopt the simple method.

E. Trial Tests: These tests were technically unsatisfactory, but we will describe them briefly for the sake of completeness. In the first test we gave the subject a card and asked him to read it aloud and then to give as many associations as rapidly as possible. An electronic circuit flashed a light if the subject paused more than two seconds between words. On this signal the card was removed and the subject was given a new card. The test consisted of 20 such cards. We expected subjects with a broadened attention to return more frequently to the word on the card, while those with a more narrowed attention were expected to associate more to their own last association. Three different raters were used in rating whether a particular association referred back to the original stimulus card or not. Suggestive changes in the predicted direction were found, but the validity of the test is questionable because of the difficulty in obtaining a consensus about the determinants of an association.

For the second trial test, we gave the subject 16 pairs of sense and nonsense words to memorize. Each pair of words was printed on a card. The cards themselves were of six different colors and contained one of six geometrical figures. At the end of the test, after the subject had been tested on his recall of the words and nonsense words, he was asked to recall as many of the colors and geometrical figures as possible. Atropine was expected to improve the recall of these peripheral cues. There was no significant change in atropine with this test, and the scatter was very small. Over a half of our subjects remembered either five or six of these peripheral factors, and the test procedure was felt to be unsatisfactory for our purpose.

V. Subjective Test Procedures.—In order to measure subjective changes produced by the drug, each subject received two interviews and a questionnaire at the time of each drug experiment.

A. Initial Interview: The initial interview was given at the time of the injection. In it we attempted to obtain a fairly detailed account of the past 36 hours in the subject's life and to evaluate recent successes, failures, pleasures, and frustrations. From these data we hoped to get some insight into environmental factors that might influence drug reaction on a particular day.

B. Questionnaire: At the end of each drug experiment, each subject was given a "forced-answer" questionnaire, containing 28 items. He was allowed six possible responses on each item. The truthfulness of an item could be rated 1+, 2+, or 3+, while three minus scores could be used to rate the falsity of it in a similar manner. For instance, the statement "my mouth feels full of saliva" was to be rated 3+ if the subject's mouth was actually full of saliva, or 3— if his mouth was extremely dry. On the other hand, either a 1+ or a 1— response was demanded on each question.

C. Postdrug Interview: Following the questionnaire, each subject was interviewed again for 15 or 20 minutes to detect any changes that might not have been picked up in the tests and by the questionnaire and to allow the subject to verbalize his feelings about the test procedures.

Secondary Experiments

Analysis of our primary experimental data from the Stroop test, the Gottschaldt test, and the Progressive Matrices showed the changes following atropine to be significant at the 5% level only if the rank changes of all three procedures were pooled. It was apparent that a larger number of subjects would be necessary to obtain more useful information from these three tests, and so we set out to get more data on these particular procedures.

A group of 16 subjects were available under certain restricted conditions. These subjects were available for only three weeks at a time, and, because of this, tests could be spaced no more than a week apart. Detailed individual studies were not feasible, and many of these subjects were not familar enough with arithmetic to take the Luchins test. With our attention restricted primarily to the three repeatable tests, however, this group of subjects promised to be a useful one, since we could set up a factorial design and be sure that all subjects would complete their tests. This had not been possible with our first group, and "dropouts" among our subjects had introduced some unevenness into the orders of drug and test administrations.

After screening these subjects to remove obviously ill members of the group, we set up a design in which the Stroop test, Gottschaldt test, and Progressive Matrices were given in all possible relationships both as to order of administration and as to drug. The tests were spaced one week apart, and all but two subjects received "training" tests on the Stroop test one week prior to their first drug test. The Luchins test and the questionnaires were administered, but we anticipated that they would not be useful in this particular population.

Scoring of "Test and Retest" Procedures

The Stroop test, the Gottschaldt test, and the Progressive Matrices were administered so that each subject could serve as his own control. In order to capitalize on this, we needed a scoring system that would allow comparison of a subject's performance on one part of a test after atropine with his performance on the other part of the same test after saline. Converting scores into ranks serves this purpose.

Stroop test scores after the first injection were ranked as one group, and the scores after the second injection were ranked as a second, separate group. Then the difference between atropine and saline ranks were taken in such a way that a positive rank change indicated an increase in Stroop time with atropine. This served the purpose of removing some of the learning effects, which remained in spite of pretesting.

Gottschaldt tests A and B were ranked separately, with ranks assigned in terms of the number of problems solved correctly. The time required for solution was used to break tied ranks. The ranking procedure was necessary on the Gottschaldt A and B tests because the raw scores for these two tests are not directly comparable, although they are highly correlated.

Progressive-Matrices scores for the even and odd sets were ranked, as were the Gottschaldt A and B. As above, ranks were given first on the basis

TABLE 1.—*Effects of Atropine on Repeatable Objective Tests*

A. Effects on Rank Orderings

Subject	Changes in Rank After Atropine: Stroop Test	Gottschaldt Test	Progressive Matrices	Sum of Changes	Subject	Changes in Rank After Atropine: Stroop Test	Gottschaldt Test	Progressive Matrices	Sum of Changes
1	23.0	−2.5	−0.5	20.0	8	0.0	−1.0	11.0	10.0
4	16.0	8.0	2.0	26.0	17	−0.5	−1.5	−6.0	−8.0
12 *	14.0	−17.0	−3.0	−6.0	3 *	−0.5	16.0	−2.0	13.5
13 *	9.0	2.5	−9.0	2.5	11	−1.0	−4.0	−2.0	−7.0
5	8.5	13.0	16.5	38.0	1 *	−1.0	−11.0	5.5	−6.5
20	7.5	6.5	13.0	27.0	11 *	−1.5	14.0	2.0	14.5
2	6.5	16.0	−1.0	22.0	15 *	−1.5	4.5	−5.0	−2.0
16 *	7.0	14.5	−1.5	20.0	4 *	−1.5	−12.0	−15.0	−28.5
10	7.0	4.0	−1.0	10.0	6 *	−2.0	−0.5	−4.0	−6.5
6	6.5	23.5	−1.0	29.0	8 *	−2.5	4.0	0.0	1.5
7	5.5	−8.0	9.0	6.5	9	−2.5	3.5	5.0	6.0
14	5.5	−5.5	−10.0	−10.5	3	−4.0	12.5	2.0	10.5
10 *	3.5	13.0	9.0	25.5	21	−4.0	13.0	−5.0	4.0
18	3.0	−21.5	1.0	−17.5	12	−4.0	1.5	0.0	−2.5
7 *	2.5	4.0	−1.0	5.5	19	−11.0	−1.5	13.0	0.5
16	2.5	2.5	−3.0	2.0	2 *	−16.0	11.0	6.0	1.0
5 *	3.5	−4.0	−1.0	−2.5	13	−21.0	−19.0	−13.0	−53.0
9 *	2.0	1.0	8.0	11.0					
15	2.0	−3.5	−16.0	−17.5	*P*	0.051	0.064	--	0.049
14 *	1.5	14.0	−11.0	4.5					

B. Effects on Means of Raw Scores

Test		After Atropine	After Saline
Stroop (mean times)	B (colors)	58.7	58.1
	C (colors-on-words)	98.0	96.2
	C-B (score)	39.3	38.1
Gottschaldt	No. correct	38.9	41.1
	Time taken	806	757
Progressive Matrices	No. correct	23.8	24.7
	Time taken	1108	1128

* Subject in second experimental group.

of total problems solved correctly, and then tied ranks were broken on the basis of time required for solution. Ranking of the Progressive-Matrices scores was necessary because, in general, performance on the odd-numbered Progressive Matrices was superior to performance on the even-numbered ones.

Results

I. Objective Tests.

A. Test-Retest Results: Table 1 shows the results on the Stroop test, the Gottschaldt test, and the Progressive Matrices. We predicted that atropine would impair performance on these tests, and the sum of rank changes showed such an effect. The effect is significant at the 5% level by the one-tail test both for the first experimental group and for the two experimental groups combined. The expanded experimental group also shows that this over-all score reflects changes in the Stroop and Gottschaldt test scores almost exclusively. Stroop and Gottschaldt changes are by themselves each close to the 5% level of confidence, whereas the Progressive Matrices scores do not even reflect a trend. A sum of Stroop and Gottschaldt rank changes is significant, with $P=0.028$, as contrasted with a $P=0.049$ for the over-all sum that includes the Progressive Matrices scores. We will return to the meaning of this finding later in the discussion. All tests of significance on rank-change data were made using Witcoxon's signed rank test for paired observations, corrected for continuity.[18]

B. Luchins Test Results: Table 2 shows the effects of atropine on the Luchins test scores. This test yielded significant results with the first experimental group, and we ran our second experimental group with the expectation that most of them would not be able to do the test at all. Only 6 out of the second group, of 16 subjects, gave usable performances on this test, for the other 10 either failed to solve some of the first four problems or gave up before finishing the test. Nevertheless, the remaining six subjects of the second group show a trend that is in

TABLE 2.—*Results for the Luchins Water-Jar Einstellung Test*

First Experimental Group		Second Experimental Group*	
After Saline	After Atropine	After Saline	After Atropine
750		710	225
625	323	630	190
610	295	230	
610	285	176	
600	243		
495	225		
330	213 †		
312	167		
257	110		
180 †	105		
175			
148			

$P < 0.025$ for first group; $p = 0.01$ for both groups.

* Only these values remained after excluding those for subjects who either "gave up" or failed to solve the first four problems correctly.

† Subject with past experience on Luchins test. Their exclusion does not appreciably alter statistical significance.

keeping with the first group, and when the data from the second group are combined with the data from the first group, the statistical significance is slightly improved. Significance was tested using White's rank test, corrected for continuity.[19]

II. Results of Subjective Test (First Experimental Group Only).

The responses of each subject on each questionnaire were added together without regard to sign to get an over-all index of subjective responses. Only one subject had more of a score after saline than he did after atropine. All of the other subjects showed a considerable increase in responses after atropine.

Inspection of the individual questionnaires revealed several interesting findings. First, all of the individual test items received greater responses after atropine than after saline. Thus, for instance, one item ("I have more of a tendency just to notice things that are around me without doing a lot of thinking") received after saline a total positive score of +8 and a total negative score of −13. The algebraic sum of these scores is −5. The sum of positive scores was +25 after atropine, and the sum of negative scores after atropine was −19. Although the algebraic score remained almost the same (+6), the absolute magnitude of responses after receiving atropine was greater by 23 points. This was characteristic. With the one exception, all items elicited a larger absolute response after atropine and a smaller absolute response after saline.

The item that received the same absolute score after both atropine and saline is in itself interesting. This one read: "I feel more anxious and uneasy than before taking the drug." It also was the only item which was significantly responded to in one direction after saline. On this item, the total score regarding sign was −23 after saline and −13 after atropine. The negative post-saline responses probably reflect the completion of anxiously anticipated injections, but the over-all results imply that anxiety diminished more after saline than after atropine.

After atropine, eight other items on the questionnaire showed responses that summed to 23 or more, regarding the signs. These eight items in themselves give a fair description of the most universal response to atropine and are presented in Table 3.

In addition to these subjective symptoms covered by the questionnaire, interviews almost invariably produced a description of dryness of the mouth. Some subjects described tachycardia, dizziness, blurring of the eyes, and drowsiness. Two of the subjects described itching of the skin; two complained of headaches, three described their sensations as being similar to being drunk on alcohol, and one subject complained of some difficulty in urinating for 12 hours following atropine.

TABLE 3.—*Subjective Responses to Atropine* *

	Statement	Algebraic Sum of Responses
1.	"I feel more thirsty."	+55 (true)
2.	"I prefer the way I feel now to the way that I usually feel."	−45 (false)
3.	"I feel sluggish and slowed down."	+44 (true)
4.	"I feel less sleepy than I did before taking the drug."	−34 (false)
5.	"I seem to be thinking about past events more than usual."	−31 (false)
6.	"If I were present in a crowd of strangers, I think it would be easier than usual for me to strike up a conversation."	−25 (false)
7.	"I think if I were driving in traffic and someone were to push ahead of me I would be more likely than usual to put on my brakes and let the person break into line."	+25 (true)
8.	"I feel more like going off and sleeping than usual."	+23 (true)

* Questionnaire items are given in descending order of algebraic sum of responses with sign of response indicated.

III. Correlations (First Experimental Group).

Because of the report by Kornetsky and Humphries,[10] we expected a positive correlation between the subjective response to atropine and the sum of objective test "changes with atropine." The observed rank order correlation is +0.20. Although this is not significant by itself, it is quite compatible with the above report.

Also, Kornetsky and Humphries reported positive correlations between objective drug responses and subjective drug responses, on one hand, and the psychasthenia (Pt) and Depression (D) scales of the MMPI on the other. Here we had strikingly negative results. None of the four possible rank order correlations even approached the significant level. Instead, they ranged in actual value from −0.16 to +0.05. Thus, there was not even a tendency for people with high D or Pt scores to respond more strongly to atropine.

Comment

I. The Broadened Attention Hypothesis.—In the section on results, we showed that atropine improved performance on the Luchins test and impaired over-all performance on the three other tests. The effects of atropine on these tests had been predicted in advance, and in both cases the results were significant at better than the 5% level of confidence. By chance alone, one would expect two separate results at the 5% level of confidence less than 3 times in 1000. Our purpose in this first part of the discussion will be to show how these test procedures were selected on the basis of our theories about the focus of attention and how the broadened-attention hypothesis allowed us to predict the effects of atropine on these tests.

Our theories about the focus of attention are covered in the first paper of this series; so we will not repeat the details here. We found that drugs and procedures which probably stimulate the reticular formation also produce narrowed attention. After these experiments we wondered if a drug known to inhibit the reticular formation would produce broadening of attention. Atropine seemed the ideal drug for testing this idea. Atropine, by inhibiting the peripheral parasympathetics, produces a picture of mild increased peripheral sympathetic activity. In this respect, it resembles drugs like methamphetamine, which produce narrowed attention. Centrally, however, the inhibitory effects of atropine on the reticular formation are well documented, but, unlike most other reticular formation inhibitors, atropine has minimal sedative effects and can hardly be considered a cortical inhibitor.[2-9]

After having decided to study atropine, we found that all of our older procedures were useless with this new agent. Size-matching performance would be sensitive to the effects of atropine on accommodation (e. g., so-called atropine micropsia). We did not want to return to the stressful loud sounds of the myographic procedure, and atropine completely obliterates the galvanic skin response. The guessing game is at present being modified for use on individual subjects, but the group procedure used in our study of methamphetamine is not practical when intramuscular injections have to be given. Faced with this complication, we began to search the literature for other procedures that might measure the focus of attention.

The first test which attracted our attention was the Stroop test, as described in the work of George Klein. In one study Klein divided his subjects into "high-interference" and "low-interference" subjects on the basis of the Stroop test performance. He described the over-all behavior of "high-interference" subjects as "reflecting perhaps determined efforts to keep judgments in line with whatever external sources of information, cues and anchors were available to the stimulus field." Except for the implication of conscious effort, this quotation from Klein is a good description of what we mean by the phrase "broadened attention," and so even

prior to the atropine studies we had experimented with the Stroop test.

For instance, using a group of 10 subjects, we studied the correlation between size-matching and Stroop performance. These subjects were attempting to match a nearby object with an adjustable image projected 200 cm. away. The final size of the distant projected image and the Stroop test score showed a rank order correlation of -0.65 ($P<0.03$). According to our interpretation, the more broadly attending a subject is, the more he will notice distance cues, the more he will correct for distance in making size judgments, and the smaller he will make the distant adjustable image. On the Stroop test, the more broadly attending a subject is, the more he will notice the printed words while trying to name colors, and the higher will be his Stroop score. Small distant object sizes and large Stroop scores correlate to give a negative coefficient. Finally, Basowitz et al.[20] reported a 2.6-second mean decrease in time for reading the third Stroop card during prolonged epinephrine infusion. Although not statistically significant, this is in the direction predicted on the basis of epinephrine-induced narrowed attention.

In preliminary experiments, we also noticed that the Stroop test shows strong learning effects, and so we felt it would be wise if additional supplementary tests designed to measure the same factor might be administered at the same time.

Klein mentioned that the Gottschaldt test was correlated with the Stroop test; Thurstone noted correlations between these two test procedures which were in the correct direction, although not statistically significant, and in preliminary tests we observed significant correlations between combined Gottschaldt A and B scores and Stroop scores. Also, on the basis of the tests themselves, it seemed logical to include the Stroop test and the Gottschaldt test in the same group. In the Stroop test, the printed names of colors are intrusive stimuli and lie outside the immediate focus of a subject's attention when he tries to name off the superimposed colors. The ability of a subject to "filter" out the interfering printed words is measured by finding out how much additional time is required to name off colors when the words are present as compared with the time required to name the colors by themselves. In the Gottschaldt test, the subject's task is to find an embedded figure hidden within a larger design. The larger design acts as a distracting factor. The process of solution consists of "filtering" out parts of the total design and comparing the remainder with the small "hidden" design. Such a "filtering" operation should be more difficult for broadly attending subjects than for narrowly attending subjects.

After adopting the original Gottschaldt tests, we became aware of the studies by Witkin et al.[21] They used a colored modification of the Gottschaldt test to measure what they called "field dependence." Witkin's "field-dependent" subjects do poorly on the Gottschaldt test and have difficulty in determining the true vertical position in the face of conflicting peripheral cues, such as sitting in a tilted room, viewing a tilted frame, or being in a tilted chair. "Field dependence" would seem very similar to "broad attention."

We found nothing in the literature to suggest that the Progressive Matrices would measure focus of attention. We included it in this group because of a positive correlation between it and the Stroop and Gottschaldt tests. The nature of the test material suggested that subjects with a broadened attention might find details of the matrices distracting. In such case, they might be unable to isolate that particular aspect of each pattern which would show how that matrix could be completed. At the same time, we were aware that the Progressive Matrices required a rather flexible approach and that it was more an intelligence test than were the other two test procedures. In retrospect, we should have used only tests with some independently demonstrated relationship to the focus of attention, because the Progressive Matrices is the only

test of the three that showed no effects from the atropine. Together the three repeatable tests showed the predicted impairment, but this is due entirely to the effects of the Gottschaldt and the Stroop test. Failure of the Progressive Matrices to detect changes after atropine also implies that atropine did not produce its effects on the Stroop and Gottschaldt tests by dulling intellectual capacity, for if this had been the case the Progressive Matrices would have been the most sensitive instead of the least sensitive test.

The Luchins test was added to our test battery as an example of a task that should be done better after atropine (i. e., with broadened attention). Narrowed attention apparently interferes with Luchins test performance. For example, Pally [17] has described lower scores of the sort we used under conditions of anxiety (i. e., stimulation of the reticular formation by "psychological" means). On this basis alone we would suspect that scores might be improved by procedures that provoke a broadening of attention, and the test itself supports such an idea. In the Luchins test, if the subject is to discover the new short method of solving the problems, he must attend to certain aspects of the task that are not essential for success with the older method. After the subject has discovered how to solve the first four problems, he may be able to solve the next four quite promptly, using the same tried and true method. In the meantime, the changed nature of the problems which permits the simpler solution may well be ignored. On the other hand, the broader the subject's focus of attention, the more likely he will be to discover the new and simpler method before he reaches the last two problems; or, failing this, the more quickly he will be able to adopt the new method when it becomes the only applicable technique. In Table 2, it is apparent that the subjects who received atropine arrived at the new method of solution more rapidly than did the control group.

In selecting tests to measure the focus of attention, we tried to avoid confusing the field of attention with the field of vision. We think of attention as focusing with respect to space, time, and meaning. With narrowed attention, the subject may readily perceive things at the periphery of his visual field if his attention is directed toward them. For example, Thurstone found no correlation between the Stroop or Gottschaldt test and his test of "peripheral span." This is not surprising because in this test of "peripheral span" the subject is directed to expect something at the periphery of his visual field.

This distinction may be made even clearer by considering one of Klein's experiments. First he selected two groups of subjects on the basis of their Stroop test performance. Then Klein made these subjects very thirsty by feeding them a specially prepared meal. Finally, these thirsty subjects were shown brief presentations of pictures with a tachistoscope. In each picture there was a central object which was designed to appeal to a thirsty person, such as, for instance, a glass of beer. The group of subjects who did poorly on the Stroop test (in our terms, the broadly attending subjects) continually had their attention intercepted by the central, highly attractive object. Their fixation tendencies were poorly patterned; they showed few peripheral fixations, and it took them longer to recognize peripheral objects. After a few trials, the group who did well on the Stroop test (in our terms, the narrowly attending subjects) were able to ignore the appealing central object and, in a more or less organized fashion, explore the periphery of each picture in the course of repeated brief presentations.

If these same experiments of Klein's are viewed alongside our Luchins test data, the differences between broadened attention and "rigidity" may be thrown into sharper relief. After repeated tachistoscopic presentations of the same slide, and after repeated questioning about what was seen, people probably develop some personal drive (i. e.,

internal motivation) to explore the periphery of the briefly exposed figures. Narrowly attending subjects did this most efficiently, and Klein spoke of such subjects as "flexibly controlled." In the Luchins test we have a different situation. The narrowly attending subjects are less efficient here, and seem "rigid" in sticking to the "complex" solution. The difference is due to the fact that our subjects had no "internal motivation" to seek a simpler solution. Our other tests (Gottschaldt, Progressive Matrices, Stroop) increase in difficulty, and this fits with the past experience of most medical students. One of our subjects actually evolved a complex "original" solution for one Luchins' problem which is insoluble by the "complex" method. This sort of behavior is somewhat different from the conventional idea of "rigidity," and our broadly attending atropine-treated subjects probably appear "flexible" because they are more likely to notice apparently unessential peripheral details.

The objective procedures that we picked to show "broadened attention" reflected the effects of atropine to a clearly reliable degree, but the subjective reports contain no consistent descriptions of changes in attention. In addition, we have found no convincing correlations between the focus of attention and the personalities of normal subjects. Psychiatric patients offer a wider range of personality traits, and studies of patients may help to clarify this problem.

In summary, if a particular task is facilitated by attention to apparently peripheral factors, then broadened attention will improve performance (e. g., Luchins test). If, on the other hand, a test demands narrowed attention, with filtering out of distracting peripheral factors, broadened attention will impair performance (e. g., Stroop and Gottschaldt tests). These changes can be demonstrated by objective test procedures, although there is little hint of such change in the subjective responses.

According to the tests used in this study, atropine broadens the focus of attention. Atropine also depresses the reticular formation, but (1) does not reduce "behavior arousal" in animals, (2) probably does not depress the cortex, and (3) from our questionnaire responses, reduces anxiety less than did saline. In other words, our data support the theory that the focus of attention is related to some activity of the brain-stem reticular formation.

The repeated failure to find any clear correlation between the focus of attention and obvious normal personality traits has been disturbing, and because of this we were particularly attracted by studies which proposed to show correlations between personality and responsiveness to drugs.

II. Subsidiary Goals.—A. Hypothesis of Kornetsky and Humphries: Kornetsky and Humphries reported correlations between the objective and subjective responses to several drugs and also between these measures of drug response and the Depression (D) and Psychasthenia (Pt) scales on the MMPI, as was described in our section on results. On calculating the correlations between drug responses and the two factors on the MMPI from our data, we failed to obtain values in the expected direction. This was surprising to us, and at first glance it appeared to conflict with the reports of these other workers. The apparent conflict is resolved, however, if we consider that the intramuscular injection of 2 mg. of atropine sulfate is a very potent physiological stimulus for the subject. These other workers reported that the degree of subjective response to 100 mg. of LSD-25 showed little relationship to MMPI scores, and they suggested that "when a severe drug effect is obtained, the personality of the subject does not play an important role. In other words, if a large enough dose of any drug were given, all subjects would respond in the same manner." [10] It seems that we encountered a similar physiological overriding of psychological factors.

In spite of this failure, we continued to make a thorough search of our interview- and psychological-test data, attempting to

find correlates of the focus of attention as measured under control conditions and correlates of responsiveness to atropine. We thought that any positive results might shed some light on suspected correlations between normal personality and the focus of attention.

Considering the large number of possible correlations that were explored, the failure to find something significant at a high level of confidence is in itself surprising. Careful study of all of our material revealed only two factors which seem worth reporting. The first observation concerns the fact that after atropine subjects gave larger absolute responses on almost all questionnaire items, although some of these "subjective changes" show no consistency from subject to subject. In other words, when a subject is aware that he has been given a physiologically potent agent, he is much more likely to describe changes in all spheres than when he suspects that he may have received a placebo. None of our subjects were "fooled" by the placebo, and it would seem that, in spite of "double-blind" precautions, an investigator is likely to get more of all sorts of subjective responses to an active agent than he is to a bland placebo.

The second finding was a suggestive correlation between objective test response and what we have called "tolerance for dependency." Dr. Eugene Myers suggested that some of our subjects might be intolerant of their passive dependent needs and if atropine produced the central neurophysiological counterpart of a passive, accepting, and nonalert state, then subjects intolerant of passive dependent feelings might find such changes extremely unpleasant. By way of compensation, such subjects might deny the subjective effects of atropine and put forth extra effort on the objective test procedures. As a preliminary test of this hypothesis, we sorted interviews into a rough hierarchy on the basis of the ease with which they discussed personal weaknesses and passive dependent needs. A high positive correlation was found between objective test responses and this ranking of tolerance for dependency. As tolerance of dependency increased, objective test impairment also increased. Unfortunately, the total number of possibilities considered makes the *post hoc* statistical testing of any such a finding questionable, and it must be considered only as a lead for future research.

B. Clinical Psychopharmacology of Atropine: The hypothetical relationship between reticular formation and the focus of attention leads us to predict how atropine will alter performance on test procedures. If the task demands a broad attention, atropine helps. If the task demands narrowed attention, atropine hinders. These effects are real, but they can be seen only as statistical changes in relatively large groups. This is partly the fault of our test material, and better measures of the focus of attention may work with smaller groups. At the same time, the statistical nature of our observations is due to the very nature of attention itself. Most likely, the focus of attention fluctuates spontaneously and also varies as values, attitudes, and interest vary. Because of this, we must recognize that while atropine probably influences behavior by broadening attention, other factors influence attention at the same time, and this effect of atropine must be observed in over-all changes of group performance.

In spite of this limitation, linking atropine with broadened attention makes us able to understand the findings of other investigators. For example, Miles[22] found that atropine decreased discriminating-reaction time. In his experiments, the time that a subject took to press a button after seeing a light or hearing a horn was increased following the injection of 2 mg. of atropine. However, when the subject had to depress one button in response to the horn and another button in response to the light, a shorter time for this discriminating reaction was found in the atropine-treated subject. Presumably, one must use a broader field of attention to discriminate between two stimuli,

and these results of Miles are understandable on the basis of a broadening of attention.

Broadening of attention is not described by our subjects, and, in fact, many of our subjects noticed no psychological changes after the injection of atropine. Some subjects described mild feelings of depression, withdrawal, or intoxication. Subjects also described a sense of detachment, with less need to respond to disturbing stimuli. If anything, ambition was reduced, and those medical students who did not go to sleep found it difficult to study after the drug injection. Perhaps this loss of focused interest is a subjective counterpart of broadened attention, although atropine probably has psychopharmacological effects on functions other than attention.

Finally, a group of responses to this drug are directly attributable to peripheral physiological effects. Almost all of the subjects noticed dryness of the mouth. On questioning, dryness of the skin, blurring of vision due to pupillary dilation and cycloplegia, and tachycardia were described. These effects would be predicted from the pharmacology of atropine, but the action of psychological factors can still be noted. Most of our subjects noticed only very slight dryness of the mouth, and few of the subjects noticed the intense dryness that surgical patients usually complain of. Several medical student subjects commented on this and thought it particularly striking in view of the contrast between the large doses they had received and the relatively small doses used preoperatively. This observation re-emphasizes [23] how the interaction between atropine and emotional state determines the final "pharmacological" action.

In summary, then, the clinical effects of atropine may be considered in three categories. The first effect is the broadening of attention, which influences performance but is not directly reflected in subjective reports. The second effect is a mild feeling of lethargy and withdrawal. The third effect is the peripheral autonomic response, marked by dryness of the mouth, tachycardia, and other parasympatholytic effects.

Conclusions

Atropine was found to improve performance on a task demanding broad attention and to impair performance on tasks demanding a narrower focus of attention. This supports a theory which relates the focus of attention and the activity of the brain-stem reticular formation. The concept of broadened attention is compared with other concepts described in the literature, and some of the problems and pitfalls associated with this concept are pointed out.

An attempt was made to find correlations between personality factors and drug-induced changes. No correlation between subjective and objective changes and MMPI factors were found. This is possibly due to a "physiological overriding" of psychological factors that resulted from the large doses used. We did observe that those subjects who seemed intolerant of their own passive dependent needs also seemed to show less objective effects of atropine. We also noticed an increased reporting of subjective change after subjects were sure they had received a physiologically active compound. Finally, the clinical psychopharmacology of atropine is described in terms of three types of reactions. These are (1) broadened attention, (2) general intoxication and lethargy, and (3) peripheral parasympatholytic effects.

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On Attempted Suicide

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Stengel [1,2] has demonstrated the validity and the usefulness of distinguishing attempted suicide from suicide. His work has opened the way to the study of attempted suicide as a separate problem and has made it necessary to question the applicability of knowledge of suicide to attempted suicide. We were stimulated by this formulation and decided to undertake a study of suicide attempts seen in a general hospital. In our efforts to understand them, we found our attention directed primarily to the motivation, the interpersonal communicative functions, and the social effects of attempted suicide.

Procedure

We studied the patients brought to the New Haven Hospital emergency room after attempting suicide between July 1, 1955 and June 30, 1956. It is customary that the psychiatric staff see these patients in the emergency room. During the year of this investigation we saw 44 people who had attempted suicide, and they comprise the series studied. They do not constitute a completely representative sample, because some of the most serious cases were not seen in the emergency room but were sent directly to surgery or to the wards, and because many of the less serious probably did not come to the hospital at all. The population studied was also not representative in that it consisted largely of lower-middle-class people, probably because they are more likely to use the emergency room. The sample is otherwise a randomly selected one. Derived as it is from general hospital emergency room visits, this population differs from Stengel's, whose investigations were carried out in a psychiatric hospital. Only 18 of the 44 patients we studied were sent to a psychiatric hospital.

We began by obtaining information in areas outlined in a previously prepared schedule from the patient and from those accompanying him while they were still in the emergency room. We sought information about the events preceding the act, the method used, the setting in which it occurred, and the ways in which others became involved. We tried to learn about how others responded to the act and about the subsequent behavior of the patient. When possible, we interviewed the patients after their emergency room visits, in the general hospital, in nearby psychiatric hospitals to which they were committed, or in our offices. We also used reports from other psychiatric hospitals and from psychiatrists in the community, including any contacts prior to the attempt. We studied the records of those patients who were subsequently seen in our psychiatric outpatient clinic and talked with their therapists. These were the sources of our observations. In studying these data, we came to regard the following areas as particularly important in the effort to understand and deal with attempted suicide.

Focal Areas in Assessing a Suicide Attempt

I. Who Discovered the Patient and How. Information about where the patient made the attempt, whether he was alone or in the presence of others, and whether others were nearby, were notified before or after the attempt, or were expected to arrive soon afterward was especially useful. In most of the attempts we studied, the patient was discovered by the person most important to him at the time. We were reminded of the way in which a dream is often told to the

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person toward whom it is especially directed as a communication. Similary, suicide attempts are often made in such a way as to facilitate discovery by the person whose reaction is of greatest importance to the patient, and toward whom the attempt is directed as a communication.

Mrs. A. had quarreled with her husband about her mother, who lives with them, and they had slept in separate beds since. The patient complained that her husband "did not treat her as a wife, would not take care of her sick mother, and did not understand her feelings toward her mother." She slashed her wrists in her husband's presence.

Mrs. B., divorced and childless, complained that her aunt received all of her mother's attention. She took 20 sleeping pills when alone in her house one morning. Her mother, who lived nearby, passed her house, noticed that the morning newspaper and milk remained on the doorstep, and, on inquiring about this, discovered her daughter.

The way in which the patient facilitates or hampers his discovery is often a significant indication of the seriousness of the attempt, and a comment on its intent.

Mr. C., recently released from jail, was accused by his wife of stealing money. She left him, taking their child with her. He got drunk, drank some iodine, and immediately telephoned his priest, who came at once and brought him to the hospital.

Mr. D., a 31-year-old married plumber, drove his car into a deserted alley and connected a hose from the exhaust into the car. He was found by a passer-by hours later and was revived at the hospital with great difficulty.

Mr. E., a 49-year-old storekeeper, took out $300,000 worth of life insurance. He then traveled 200 miles from his home and family, registered in a hotel, went to his room, and shot himself through the head with a rifle. He was discovered by hotel personnel, brought to the hospital, and, after a series of surgical procedures, just survived.

Some of the attempts we studied were made in such a way that the patient's being discovered and saved was entirely dependent on an active demonstration of concern by a person important to him.

Mr. F.'s wife began having an affair with another man and made little effort to conceal it, frequently staying out all night. She threatened to leave him and walked out of the house. He got drunk and slashed his radial artery. His wife did return that night, found him, and brought him to the hospital.

This attempt might be regarded as a "test of love." It was carried out in such a way that the patient staked his life on his wife's return. By returning, she demonstrated her love and saved his life.

II. Precipitating Interpersonal Crisis.—Using the information elicited in the emergency room from the patient and from those accompanying him, we tried to obtain a picture of his situation prior to the attempt. We often found that a crisis had been reached in a struggle between the patient and the same person toward whom the attempt was directed.

Mrs. G., age 32, was divorced by her first husband when she became pregnant by Mr. G. Her first husband was granted full custody of their two children. Soon after the divorce she began living with Mr. G. Their child was delivered prematurely and died. During the following year she worked as a salesgirl in a ten-cent store. Her stepfather lived here; her mother, in Cleveland. Mr. G., now her common-law husband, worked as an elevator operator in the hospital. He drank heavily. He complained about her brooding over the death of their child and wondered whether she was faithful to him. He quarreled with her frequently and began to neglect her. Alone in their rooms early one Sunday evening, she drank four cans of beer, telephoned her stepfather, and told him that she was going to kill herself. She then swallowed a handful of acetylsalicylic acid tablets and the contents of a small bottle of lighter fluid. Her stepfather telephoned her landlady, who called the police. They found her sitting in a chair staring at the ceiling and took her to the emergency room. She told the doctors: "Now I've ruined everything. My husband's family will know we're not married. My stepfather will know. My husband and I will lose our jobs." The doctors contacted her husband and stepfather, neither of whom wanted to come to the hospital. Mr. G. was worried about losing his hospital job, but finally came. They embraced. In a few minutes they were arguing about what should be done She was admitted to the general hospital for observation. There she told the doctors that her common-law husband had never divorced his previous wife, and explained: "He doesn't want to go through with divorce proceedings because of the disgrace it would involve." Her mother, informed of these events by her stepfather, was concerned about her daughter having tried to do away with herself, came here from Cleveland, and took the patient home with her. Mrs. G. has been living with her mother since. The crisis in the struggle with her common-law husband was resolved, following the suicide attempt, by her mother's response to it.

Prior to the attempt and at the time of the attempt, the patient was characteristically involved in a desperate search for evidence of the concern and understanding of those important to him.

Mrs. H., aged 20, was angry with her husband because he spent many of his free evenings visiting his sister, leaving his wife behind to care for their 2-year-old son. He often bought toys for his son but refused his wife's requests for money to buy new underwear. She was ashamed to ask her mother to buy underwear for her and could not bring herself to take money for this without her husband's specific permission, even though she managed his pay check each month. After an argument with her husband, in which he again refused to give her money for underwear, and in which she angrily protested that he cared more for their son than he did for her, she went to the bathroom and swallowed a handful of sleeping pills. She was committed to a psychiatric hospital. On his first visit to her there, he brought her a new petticoat. She was discharged soon afterward.

III. "Desired Effect" of the Attempt.—We found that the patients' life situations changed markedly after their suicide attempts. For example, the following changes occurred in the lives of the patients cited thus far.

After Mrs. A.'s suicide attempt, she found it possible to talk things over with her husband. He agreed to accept more responsibility for her mother, and she was subsequently willing to consider having her mother move out of the house.

After Mrs. B.'s attempt, her mother left the aunt and moved in with Mrs. B.

After Mr. C.'s attempt, his father and his father-in-law found him a job and helped him effect a reconciliation with his wife.

Mr. D. was committed to a psychiatric hospital for long-term treatment after his attempt.

Mr. E.'s shooting himself had the effect of a partial decortication. He has remained invalided and has required complete care since.

Mr. F. was committed to a psychiatric hospital after his attempt. His wife said that she would wait for him and that she would stay with him "if he got better."

Mrs. G. was taken home by her mother after her attempt and terminated the relationship with her common-law husband.

After Mrs. H.'s attempt, she was committed to a psychiatric hospital. Her husband brought her a new petticoat when he visited, and she was discharged soon afterward.

The important changes in the life situations of the patients following their suicide attempts were usually brought about by the people most important to them, and they were often changes clearly desired by the patient prior to the attempt.

Mrs. I., a 42-year-old woman with three young children, complained about her husband working at night. He drank heavily and showed little interest in her and the children. She took a handful of sleeping pills. Following the attempt, her husband joined Alcoholics Anonymous and for the first time in the 14 years of their marriage obtained a daytime job and gave up his nightwork as a bartender.

Mrs. J., age 27, with three children, was being divorced by her husband, who planned to go to New Mexico on a new job without her. She slashed her wrists and lacerated her face and chest with a razor. Her husband acceded to her pleas, gave up his plans for a divorce, and took her and the children with him.

When we realized that changes desired by the patient prior to the attempt frequently came about as a result of the attempt, we began consistently to look for changes desired prior to the attempt, and to see whether or not these changes were effected. We found such "desired effects" in 36 of the 44 cases we studied. In 34 of these 36 cases the "desired effects" were actually brought about through the attempt. We regard these 34 attempts as successful in the sense that desired changes in the life situation of the patient occurred as a consequence of the attempt, perhaps a more appropriate criterion for designating the success or failure of a suicide attempt.

The desire for these changes was often clearly expressed prior to the attempt, and efforts to bring them about by other means had frequently been made.

Mrs. K., age 27, with five children, had stopped working in her husband's butcher shop early in their marriage, after she had been accused by her father-in-law of stealing money from the cash register. Her husband regarded her requests for money to buy clothes for the children, to furnish their home, and to take the children on a vacation as excessive. He contributed to the support of his brother and two sisters. While he was preparing his income tax return, Mr. and Mrs. K. argued about money for two days. Finally Mrs. K. told her husband that she would leave him, taking two children with her and leaving three with him. He threatened to put these children in

an orphanage. She first sought help from a family agency but could not be seen immediately. She then called her family doctor, told him that she was having trouble sleeping, and asked for some sedation. She picked up the small supply he had prescribed for her, and, having decided "to die rather than see my children in an orphanage," she swallowed eight sleeping capsules. Following the attempt, her husband insisted that she take a long vacation at an expensive resort, and he hired a part-time maid to help out with the children, despite her protests that "he could not afford all this."

Mrs. L., age 43, mother of three children, had been nervous for many years. She had recently become more upset and depressed, and wanted now, as previously, to see a psychiatrist. Her husband opposed this plan vehemently. Mrs. L. took 8 acetylsalicylic acid tablets and, later, 12 sleeping pills. She was brought to the emergency room by her husband, who then proceeded directly to arrange for psychiatric treatment.

The changes which followed these suicide attempts were sometimes transient and at other times appeared lasting. We found that of the 34 cases in which desired changes were effected, the changes occurred only transiently in 18. In 16 they appeared more lasting, at least through the period of our follow-up study, which varied in length, with different patients, from 10 to 18 months.

IV. "Desired Effect" and Hospitalization.—Of the 44 patients, 18 were hospitalized after their suicide attempts, 13 directly from the emergency room and 5 within six weeks of their attempts. In 3 of the 18 cases, hospitalization itself was part of the "desired effect" sought in the attempt.

Mrs. M., age 28, was at home with her mother on Christmas Eve on a two-day pass from a mental hospital, in which she had lived for seven years. After an argument with her mother about her smoking, she took 30 acetylsalicylic acid tablets, was brought to the emergency room by her mother, and was returned to the mental hospital.

A "desired effect" was discernible but not achieved in two cases. Both these patients were among the 18 hospitalized as a result of their attempts. Seven of the eight patients for whom no "desired effect" other than death could be discerned were hospitalized as a result of their attempts. The eighth patient in this group had made his attempt in jail and was returned to jail after being seen in the emergency room. A clear relationship between "desired effect" and hospitalization thus emerges: Both the patients who did not succeed in achieving their "desired effects" and seven of the eight patients for whom no "desired effect" other than death could be discerned were hospitalized. Of the 18 patients who were hospitalized, 6 also achieved their "desired effect." Five of these six were hospitalized only briefly.

V. Severity of the Attempt.—We rated the severity of the 44 suicide attempts studied on an arbitrary scale from 0 to 5. In assessing their severity we took into account the method used, how badly the patients were hurt, how they were discovered, and the behavior and comments of the patients and of those accompanying them in the emergency room.

Mrs. N., age 48, was angry with her husband because he worked late and because she felt he was unfaithful to her. She telephoned him late in the evening at his store and told him that she had tried to end her life by swallowing Lysol and Dexamyl * tablets. Gavage was done in the emergency room, but no evidence of her having ingested either substance was found. She told doctors that her attempt was a bluff to get even with her husband and to scare him. She had frequently threatened to commit suicide in the past. The severity of this attempt was the only one in the study rated as 0.

Mr. O., age 57, widowed with five children, was upset about his youngest daughter's having an affair with her uncle, and having become pregnant by him. Alone in the house on a Sunday evening, he cut his left wrist deeply with a razor blade. As he began feeling weaker and frightened, he telephoned his daughter and told her what he had done. She brought him to the emergency room. The severity of this attempt was rated as 3.

Mr. P., age 46, had been a skilled railroad worker for years. He had been unemployed for six months after he developed obscure genitourinary symptoms with severe, debilitating pain and impotence. He was obsessed with thoughts of whether or not his only daughter was still a virgin. On a long holiday weekend, he shot himself in the left chest but missed his heart. This attempt was rated as 5.

In grading the severity of the 44 attempts studied, 4 were placed in the severest category, rated as 5; 7 were given a 4 rating;

* Each tablet contains 5 mg. of *d*-amphetamine sulfate and 32 mg. of amobarbital sodium.

12 a 3 rating; 10 a 2 rating, and 10 a 1 rating, and the severity of a single attempt was considered 0. The classification of the attempts on the basis of these ratings of their severity was correlated with (1) the sex of the patient, (2) the descriptive diagnosis made by the psychiatrist in the emergency room, (3) whether or not a "desired effect" of the attempt other than death could be discerned, and (4) whether or not the patient was alone at the time of the attempt.

1. Sex and Severity: The 44 patients included 11 men and 33 women. All of the severest attempts, those rated as 5, were made by men. Of those rated as 4, three were by men and four by women. The group rated as 3 consisted of 10 women and 2 men. All 10 of the group rated as 2 were women. There were eight women and two men in the group rated as 1, and the one attempt rated as 0 was made by a woman. This preponderance of men making severer attempts and of women making less severe attempts is in keeping with the findings of other investigations.[3,4]

2. Diagnosis and Severity: A descriptive psychiatric diagnosis of psychosis was made in the emergency room in 13 of the 44 cases studied. All four of the severest attempts, the group rated 5, and four of the seven rated as 4 were among the patients labeled as psychotic. Only two with a 3 rating, one with a 2 rating, and two with a 1 rating were so diagnosed. We were able to confirm the diagnosis of psychosis in 10 of these 13 patients by both prior history and behavior other than the attempt itself. Of the other three attempts, where verification of the diagnosis was not possible, one each was rated as 5, 4, and 3. Thus, a majority of those patients whose attempts were rated as severe were also among those diagnosed as psychotic.

3. "Desired Effect" and Severity: In 8 of the 44 cases studied we were not able to discern what we have described as a "desired effect" of the attempt. Of these eight patients, three had ratings of 5, two had ratings of 4, and three had ratings of 3. A "desired effect" could be discerned, however, in some of the other severe attempts and in all of the less severe attempts. The attempts where we were not able to discern a "desided effect" were all relatively severe, and it is probable that in these attempts death was the intent. Seven of those eight patients for whom a "desired effect" other than death was not discernible were diagnosed as psychotic. Whether or not a "desired effect" could be discerned and whether or not it was achieved was therefore closely related to the severity of the attempt.

4. Severity and Being Alone: Of the 44 patients studied, 18 were alone at the time of their attempts. Eight other patients, though alone, are not included in this group because they notified others at the time of their attempt. The 18 who were alone and who did not notify anyone included 3 of the 4 patients whose attempts were rated 5, five of the seven with a 4 rating, 7 of the 12 with a 3 rating, only 1 of the 10 with a 2 rating, and 2 of the 10 with a 1 rating. Thus, the severer the attempt, the more likely is the patient to have been alone at the time of the attempt.

VI. Immediate Responses of Others to the Attempt.—We tried to assess the immediate reactions of others to the patient and to the attempts. We relied on the reports of the patient, of those accompanying him, and on the psychiatrist's observations in the emergency room. We were particularly interested in the responses of those accompanying the patient and of the hospital staff. We distinguished three major immediate responses: (1) concerned and sympathetic, (2) calm and relatively indifferent, and (3) punitive and counteraggressive. The reactions of the hospital staff to the patient often paralleled those he evoked from persons important to him. This was seen both when an unmixed reaction was forthcoming and when more complicated reactions, including contrasting responses, were elicited. There was a tendency, however, for shifts in the reactions of the hospital staff to be different from shifts when they occurred in the re-

sponses of the important persons. Whereas an initially counteraggressive response from the immediate family would sometimes shift to one of concern, the physicians and nurses treating the patient would more frequently shift from an initially sympathetic response to one of annoyance. This seemed to happen when they came to regard the problem as medically less serious. We were impressed with the usefulness of observing the responses of the hospital staff as an indication of the reactions likely to be evoked by a given patient, even though the hospital staff's involvement with the patient was transient and less intense.

These immediate responses are of importance in dealing with suicide attempts because of the indications they offer of whether or not a given attempt will be followed by desired changes in the patient's life situation, and hence of whether or not the needs which brought about the attempt will continue to operate.

In 22 of the 34 attempts where the "desired effect" was achieved, the immediate response shown by at least one important person was concern and sympathy. This response is illustrated above in the cases of Patients A, B, C, F, G, H, I, J, and K.

In 11 of the attempts where the "desired effect" was achieved, at least one important person responded initially with calmness and indifference. Achieving the "desired effect" in this group depended either on other persons who did not respond with calmness and indifference (five) or on a subsequent change from this response to one of concern (six).

Counteraggressive and punitive responses were evoked from at least one person important to the patient in 11 of the cases in which the "desired effect" was achieved. Here, again, achieving the "desired effect" of the attempt depended on a change in this response (six) or on other persons whose response was not counteraggressive or punitive (five).

Mrs. Q., aged 68, a lonely invalid, attempted suicide one morning by lying on her kitchen floor with the gas stove left on after stopping up the windows and the door. She was found an hour and a half later by her sister, whom she had expected for lunch. The patient's husband, a busy physician, spent little time with his wife. In the emergency room, he said that his wife had talked frequently of being depressed and of suicide. "She used to ask me all the time about which is the best way to kill yourself. I always told her that jumping from a window of a tall building was best. I don't understand why she tried it this way."

Of the only two cases in which a "desired effect" was discernible but not achieved, the response elicited was consistently calm and indifferent in one and consistently punitive and counteraggressive in the other.

Mr. R., age 23, the youngest of four, had failed to win his father's admiration when he was the only one of his sons to graduate from high school. Instead, his father encouraged an older brother to "give him a licking to show that graduating didn't make him as important as he thought it did." The patient joined the Army but was discharged after a psychiatric hospitalization. On returning home, he was unable to get a job. He felt close to his mother, but she grew impatient with his leaning upon her and left for an extended visit with her sister. He was left with his father and brothers. They taunted him about his not working. He went to his room and slashed his wrist. His sister called up to him to bring a chair down to her in the back yard. When he brought it to her, she noticed a blood stain on it and asked what had happened. He said that he had scratched his wrist on the chair. She angrily grabbed his hand, saw the razor cut, and screamed at him for being stupid and a liar. On hearing what the patient had done, his father said: "Why didn't you take a car and drive it off a bridge and smash it up and really kill yourself?" In the emergency room he was asked why he had cut his wrist. "I did it to satisfy them," he explained. Psychiatric hospitalization was recommended, but the patient returned home instead. Six weeks later, however, he voluntarily sought hospitalization. He was soon placed on a disturbed ward and remained there for over a year.

We have emphasized the usefulness of observing the responses to the attempt of persons important to the patient. In cases where no "desired effect" other than death could be discerned, however, the observation of these responses was not particularly useful. Here a sympathetic response did not presage a change in the situation which led to the attempt, confirming the impression that these patients were not primarily moti-

vated in their suicide attempts by an effort to influence others.

Comment

In studying these suicide attempts, we observed a characteristic sequence of events culminating in the achievement of what we have termed their "desired effects." The patient was involved in a struggle with the persons important to him and sought a modification of their attitudes or a specific change in his relationships with them. After a crisis was reached in this struggle, the patient sought to effect these changes through a suicide attempt. The changes sought were sometimes described directly by the patient. At other times the patient was not conscious of his seeking these changes, or he denied them, but they were clearly revealed in his behavior. Patients sometimes told of seeking such changes prior to their suicide attempt, of seeking them through the attempt, and by still other means afterward. We discerned the precence of these "desired effects" in 36 of the 44 patients investigated, and in 34 cases documented the actual occurrence of the changes sought following their attempts.

We have been primarily concerned with the observation of the effects of attempted suicide and with the patient's motivation in his relationships with persons important to him. Our observations suggest that the importance of this kind of motivation in the attempt is related inversely to both the severity of the act and the use by the patient of psychotic mechanisms. From these observations, a continuum emerges. With regard to severity, it ranges from the patient who pretended that she had attempted suicide, when no such action had been undertaken, to the patient who, in isolation, carried out an attempt which had as its aim his total destruction and which resulted in his partial decortication. This continuum overlaps with a second, which ranges from motivation consisting largely in an effort on the part of the ego to effect changes in relations with others, to motivation of a largely primary process character. Thirdly, this continuum ranges from psychopathology characterized largely by neurotic mechanisms used interpersonally by a relatively intact ego, to psychotic mechanisms used in a regressed state, where the boundaries of the self and the outer world are unclear and where interpersonal motivation of the order described is not present. Fourthly, it ranges from the suicide attempt which is essentially self-preservative, directed at mobilizing support from others and at effecting life-supporting modifications of a previously intolerable situation, to the attempt which consists predominantly in the directing of aggressive and destructive impulses toward the self, as well as toward others. This fourth continuum is characterized in the middle of its range by a fusion, a delicate balance of self-preservative and destructive impulse derivatives. Here a suicide attempt may serve as a "test of love." It is like a trial by fire, with the person's life staked not upon "fate" but, rather, upon a demonstration of love by those important to him through their efforts to save him. If they prove that they care, he lives. If they fail to demonstrate their love, he dies; and they will suffer consequences too. Weiss [5] has suggested an analogy between this gamble and Russian roulette. However, the patient may stack the cards more or less heavily against his living. Russian roulette may be played with from one to five bullets in the chamber.

These observations, while emphasizing the interpersonal determinants and effects of suicide attempts, also comment on the intrapsychic representations which are inseparable from them: The patient's ambivalence regarding important objects is expressed by his seeking, in the same act, to move closer, to love and to be loved by them, and, at the same time, to inflict suffering and guilt upon them and to destroy them. The patient's ambivalence toward himself is expressed in his carrying out an act of self-destruction, while seeking in its very performance the preservation of his life and new strength from the love and support of others.

In trying to understand the motivation and the effects of attempted suicide, we sought to clarify its primary and secondary gain. The extent to which preexisting intrapsychic conflicts are resolved by an illness, a symptom, or an act is customarily regarded as its primary gain, and the gratifications accruing from an illness after it has been established are considered its secondary gain. By these definitions, according to which primary gain is limited to the resolution of intrapsychic conflicts, what we have described as the "desired effect" in attempted suicide would have to be considered part of its secondary gain. However, Freud [6] clarified these concepts in a note added in 1923 to his "Fragment of an Analysis of a Case of Hysteria." Here he distinguished between "internal or psychological" (intrapsychic) and "external" (interpersonal) components in the primary gain which combine in bringing about the symptom or illness. Secondary gain is then limited to those incidental, unexpected gratifications accruing after the illness, symptom, or act has been established or completed, and which did not contribute to its occurrence. According to this expanded definition, those social effects of attempted suicide which we designated as "desired effects" would be part of the external component of its primary gain rather than its secondary gain. The dividing line between external primary gain and secondary gain is sometimes blurred, however, and the distinction will depend on the observer's judgment as to whether an effect was desired, consciously or unconsciously, or whether it was unsought and unexpected.

The consideration of these intrapsychic and interpersonal functions of attempted suicide, and of its primary and secondary gain, emphasizes the importance of the intent of the act. We have referred to the usefulness of thinking about and studying attempted suicide separately from suicide. In our view, however, the distinction between them should be made on the basis of the intent of the act rather than on the basis of the outcome of the act. A person accidentally killed because the rescue he had anticipated was not carried out would, on the basis of intent, be considered an attempted suicide. On the other hand, Mr. E., who shot himself in the head, would be regarded as a suicide, although the act accidentally miscarried. When suicides and attempted suicides are differentiated in this way, attempts in which the intent remains unclear still lie somewhere in between. This group includes the attempts we have designated as "tests of love," where the patient in effect renounces the decision, leaving it for others to decide for him whether he will live or die by the way in which they respond to the act.

Unfortunately, our limited knowledge often does not permit the accurate assessment of conscious and unconscious motives. When it is possible to make this distinction, we would designate as "attempted suicide" acts intended by the patient to modify his life situation, and as "suicide" acts where death was the intent. Such a distinction on the basis of intent is useful in the disposition and treatment of suicide attempts, and is often made in practice when deciding whether a patient requires hospitalization. In examining our 44 cases, we find that of the 8 persons for whom no "desired effect" other than death could be discerned, 7 were hospitalized, 7 were diagnosed as psychotic in the emergency room, and all 8 were among the severer attempts. Whether or not a "desired effect" other than death can be discerned in an attempt offers an important indication of whether, in terms of intent, the act is a suicide attempt or a suicide, and is therefore important in deciding how the patient should be treated. Another important guide in determining the disposition of the patient is provided by the effects of the attempt. If a discerned "desired effect" has been achieved, the crisis leading to the attempt has been, at least temporarily, resolved.

The occurrence of these "desired effects" will also produce a realignment of forces

intraphysically which may be observed in the behavior of the patient following his attempt. Such a realignment, derived from the responses sought and obtained from important persons, may be responsible for some instances of what have clinically been described as "rebirth phenomena" in attempted suicide, a sudden, radical change in mood and affect following the act.†

The distinction we have suggested between attempted suicide and suicide, based on intent, evolved from, and has brought us full-circle back to, a recognition of the importance of the patient's ambivalent involvement with others. This emphasis upon the patient's intense relationships with others stands in contradistinction to the emphasis on the patient's isolation by Durkheim [7] and Stengel.[2] Most of the suicide attempts we studied were made not by isolated people but, rather, by persons actively engaged in a struggle with others important to them. Isolated people tended more toward suicide.

This difference between the patient's involvement with others in attempted suicide and suicide is confirmed by the observation that 29 out of the 44 attempts studied occurred on either a weekend or a holiday, thus ensuring the presence or the availability of persons important to the patient. The other 15 attempts included a larger proportion of patients for whom a "desired effect" other than death was not discernible. Attempted suicide requires the presence of those at whom it is ambivalently directed, whereas suicide demands their absence.

We have described attempted suicide as a response to a crisis involving the persons important to the patient. This raises the question: Why did the important people not respond to the patient's other pleas, and yet respond positively to the patient after a suicide attempt? A suicide threat is a drastic and powerful weapon, even more effective when it is acted upon. The successful use of such threats seems to depend on the involvement of the person toward whom they are directed, and the potentialities of mobilizing their guilt and of playing upon their unconscious death wishes. The characteristic interactions of our 36 patients with the persons important to them seem to have been of a kind that required such drastic steps. This may be related to the lower socioeconomic status of these patients, where there is a premium on actions rather than words, and where relatives seem deaf to appeals which in another social class might not go unheeded. Just as the ratio of attempted suicide to suicide is not the same for men as for women, it may also differ with social class and cultural background.

Another question concerns the patient's choice of attempted suicide as the means of dealing with the crisis confronting him, rather than by developing a neurosis, a psychosis, or a psychosomatic disorder. A suicide attempt is distinguished from these other possible responses by its volitional character. It is more clearly a choice, an act evolving from a decision. Another characteristic of attempted suicide, also shared by other forms of "acting out," is its spiteful character. It is directed at mobilizing the guilt of those emotionally involved with the patient through an act which hurts the patient himself. The problem of specificity in this "acting-out" group of disorders requires study. The active nature of this effort at resolution is more conspicuous than are the volitional elements in "becoming" neurotic or psychotic, or in "developing" a psychosomatic illness. In that group of attempted suicides which we have designated as "tests for love," however, the patient to some extent relinquishes this active role and forces others to make the decision of living or dying for him. The patient's ambivalence toward the persons important to him, characteristic of suicide thoughts and acts, is particularly evident in this group of patients.

In summary, we have come to regard attempted suicide not as an effort to die but, rather, as a communication to others in an effort to improve one's life. The evaluation

† Dr. Alfred Gross looked to the elucidation of these "rebirth phenomena" as one means of gaining a clearer understanding of suicide.

and treatment of a suicide attempt require an assessment of its intent. We have emphasized the usefulness, in making such an assessment, of trying to discern a "desired effect" and of determining whether or not a "desired effect" has been achieved. We have been impressed with the frequency (34 of the 44 cases studied) with which desired changes in the life situation of the patient were brought about as a result of their attempting suicide.

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"The Old Timers' Club"

An Autonomous Patient Group in a State Mental Hospital

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Recently there has been a reawakening of interest in the formation of patient groups in mental hospitals. The focus has been their meaning to the patients and their value as therapeutic instruments. One area that has been the subject of little investigation is the autonomous patient group—its functions, meanings, and areas of communication. Such an autonomous group developed at the Chicago State Hospital * and functioned for some time. Its history reveals something of the significance of such a club to the patients and some further insight into the therapeutic and antitherapeutic attitudes of hospital personnel.

History

Early in 1950 an occupational therapist, having had some success in organizing patient groups previously, decided to try the same thing at the Chicago State Hospital. She chose isolated, uncommunicative, chronic hospitalized patients who were (1) parole patients, i. e., had the freedom of the hospital grounds, and (2) engaged in no specific hospital chores or activities. She saw them as "lonely old men standing around, not talking to one another," and decided they should be brought together. To implement the organization of the group, she chose an active verbal patient (A.), whom she described as "having sentimental ties with personnel and patients." He had been hospitalized since 1941, with a diagnosis of dementia praecox.

The purpose of the organization as seen by the occupational therapist was one of service, e. g., to make signs for use about the hospital grounds, to help publicize clean-up and fire-prevention weeks, to direct more confused patients, and, lastly, to help one another. The club members did engage in such service activity, but gradually focused on the last goal—to help one another. This was verbalized as wanting "to help patients who are hurt and lost." They picked the name "The Old Timers' Club," although membership consisted of patients who had been in the hospital for as little as 3 months and as long as 33 years. The structure of the club was democratic; minutes of the meetings were kept; dues were paid as members were able (10-25¢ monthly); membership pins and cards were issued; plays and musicals were given for the other patients; occasionally the club was able to afford an outside speaker, e. g., a Y. M. C. A. lecturer who showed a travel film and discussed it, and they visited physically ill members in the infirmary and brought them gifts purchased with club dues. The occupational therapist remained in the background, giving advice on parliamentary procedure, while the president of the club attempted to implement the decision of the majority of the members. Association with other personnel was incidental. On one occasion a doctor took a group of club members to a baseball game. There were requests by the members to bring locked-ward patients to the meetings or to entertain on such locked wards, but it is not clear whether this occurred at the time.

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* Dr. Kalman Gyarfas, Superintendent, Chicago State Hospital, gave permission for, and cooperated in, this study.

In the spring of 1954 the members voted to give a magnolia tree as a present to the hospital. This tree was chosen because of its permanence and the fact that it bore leaves all year round. It was planted on the grounds, with a sign announcing the donor. The members also suggested buying books and a world globe for the hospital's patient library. In 1954 the president of the club was discharged from the hospital and, although still paranoid, was able to make an acceptable social adjustment outside the hospital. Prior to organization of the club, this patient had repeated agitated episodes requiring physical therapies, but none were reported after he assumed leadership of the club. The club elected a new president (B.), who had been hospitalized in 1943 and again in 1946, with the diagnoses of catatonic and paranoid schizophrenia. Membership was now 47 and was considered desirable and sought after. Prospective members could only be introduced by accepted members and then voted upon for admission. What was most apparent about the club at that time was that its implicit purpose, to help one another, had survived, whereas its explicit purpose of service was no longer evident.

In the fall of 1954 the club was removed by vote of the membership from the physical plant of the occupational therapy department, where time, space, and activity were restricted, to a seldom-used room of an administrative building. The members were able to use these facilities because the president, working on the grounds detail, had access to the key of this little-used room. The insistence of the director of the occupational therapy department that the rules be strictly enforced, i. e., no occupational therapy worker could be engaged in activity outside the occupational therapy department facilities, meant that the occupational therapist could not continue with the club as part of her duties, and so she was gradually forced to withdraw her interest. The administration tacitly accepted the use of this room by the patients, assuming that if they had entry to it, someone in whose care that building was must be supervising the activity. Thus the club became autonomous.

Without supervision, the hours of the club were expanded from 8:30 a. m. to 9:00 p. m.; female patients began to take part in the club activities and were made members by vote; some members presented themselves on locked wards and took more disturbed patients to the club room and returned them after meetings; some members kept newer, cleaner clothes at the club room and wore them during meetings; two kittens were kept there as pets (as one patient (C.) said, "You have to learn to treat animals right before you can do it with humans"); a miniature printing press was purchased with some of the collected dues and used to make up membership cards and other announcements that the club thought important; the club gave parties in basement areas from time to time; food was obtained through informal channels, and then certain key administrative personnel were invited; the business manager of the hospital was sought out for advice, and a television set reached the club room through unofficial channels from the business office of the hospital.

The club room gave added permanence to the organization. A sign was painted and placed on the wall above the door, announcing in large black letters "The Old Timers' Club." Some members would sit there most of the day, sometimes completely uncommunicative. Their belongings began to collect, as there were few other places about the hospital campus where personal belongings could be kept. There were clothing, papers, club records, stationery, painting supplies, and other items with special meaning to individual members.

The president was reported to have become grandiose in his ideas for the club. His behavior, however, was still acceptable to the club membership, and to the administration personnel for whom he continued doing his work.

The attitudes of the personnel who knew about the existence of the club, and who were questioned, were as follows: For some, approval of the club fitted into their own needs to do good for some patients in the relatively barren life at the state hospital; for a few, its usefulness was questioned, for it seemed to them to enable the patient to settle down to a more comfortable, but not therapeutic or progressive, existence in the state hospital, but for the majority, the club was tacitly accepted and its implications ignored as long as its purposes *seemed* to conform to the hospital's custodial setting.

After December, 1954, when a change in administration occurred, a number of events happened in the hospital community. The staff became increasingly disturbed as an active therapeutic approach to the hospital population was initiated. Several sources of self-esteem seemed jeopardized. On one ward psychologists began a study concerned with the effectiveness of an increased therapeutic milieu, and used a second connecting ward as a control. A resident training program was started, and, where once the patient had been the absolute preserve of the attendant and occasional interested doctor, he was now being approached and "stirred up" by a variety of people. The change in the hospital from a custodial to a treatment milieu, and the fact that a basic difference between patient and staff was no longer postulated, were sources of anxiety to personnel. With this change in the hospital's goals, some of those who tacitly accepted the club previously were now uncomfortable about its activity.

An employee who previously had a benevolent attitude toward The Old Timers' Club, having on occasion given them privileges, had difficulties with the administration, which reached a crucial point late in 1955. He had been demoted a number of times because of difficulty in dealing with his subordinates and now dealt almost exclusively with patients who worked on various details about the hospital. The activities of the club were now identified with the new, more active administration, and some of his anger at his loss of status was first shown in a punitive removal of the television set from the club room.

In December, 1955, after a routine fire-hazard warning had been issued after a check of the club area by a hospital fire department employee, the accumulated possessions of The Old Timers' Club were removed and incinerated. The speed with which the order was carried out was a partial result of the previously mentioned employee's difficulty, as well as some increase in the fire department employee's concern with cleaning up following the death of his wife. This all occurred without consultation of the club members, and apparently without warning. The response of the members was instantaneous. Some of them ran to the incinerator trash pile to see if they could salvage any of their belongings. The only item saved was the treasurer's log book, which was hidden and given to us at the time we investigated the club. The president, although delusional before, now became more so, and was in addition agitated and assaultive, so that he had to be placed on a maximum security ward. His major delusion now consisted of the idea that his father had been president of the club and had been electrocuted. He felt that now he was being punished for his father's crime of being associated with the club. He would discuss the club only in this displaced manner. The business manager of the club (D.) spoke in a word salad. One of the female members of the club (E.), who had been most interested in the care of the kittens, went to the assistant administrator of the institution and asked for the key to reopen the club room. Although given the key, she became mute and resistive, necessitating transfer to a locked ward for a time. A number of the members became less communicative, and others seemed confused. One member attempted to start a chess and checker club in its place, but was unsuccessful.

It was at this time that we learned of the club. We sought out a patient who was reported to have been an "Old Timer" (F.). He was grandiose and delusional but gave a coherent history of the club. The next day a second patient came looking for us in the admitting ward. He had overheard F. speaking of two doctors who were interested in The Old Timers' Club and came to tell us of his role in the organization. The following day groups of two and three patients appeared, each with a spokesman who told about their recollections of the club and its specific meaning to them. In some of these groups only one man, the spokesman, was able to speak coherently; yet members of the entire group were able to communicate with one another, if not directly with us. No two groups had directly communicated with one another, and yet in this indirect way the hospital grapevine had spread the word of interest in the club.

All of these patients asked if we would reorganize the club. Five members spoke of the club's having been in existence for over 10 years, with as many as 80 members, but no corroborative information could be obtained from personnel or other patients.

The various members told of the club's meaning to them in the past. (G.) "It was a place where I could work without interruption, not for just an hour, like occupational therapy. I had somewhere to store my paints and belongings." (H.) "It was a place to go where you didn't have to stare at four walls all the time; you can't get well staring at four walls." (I.) "A place to work on ideas that the hospital could help with." (J.) "Where you could sit and talk with friends, or do nothing." (G.) "It was a place where the attendants weren't down on your neck all of the time." (K.) "A place to help backward patients come out of their shell. A place where people want to belong." It was indicated that the club had some further special meaning, as though the sum were greater than the whole of its constituent parts, i. e., the individual members. When discussing the ownership of the club funds ($11.25), one patient (I.) said: "It belongs to the club, not the members," and another patient (F.) said: "There should be clubs for everyone, doctors, nurses, and patients. It's a way of keeping together." The patients felt that the club had been closed by the administration for a variety of reasons, but all of them indicated that the administration could be arbitrary about such things. It was felt (*a*) that the reasons were good but incomprehensible to the patients, (*b*) that the patients had done something wrong for which they were being punished, (*c*) that some kind of impropriety, probably sexual, had occurred or was suspected, (*d*) that the president had exceeded his authority, (*e*) that there was some reason related to a specific club member (e. g., [L.] "I guess it was because I did too much decorating in the club room"; [F.] "Because I wasn't there as sergeant at arms"), and (*f*) that there was no good reason. Reason (*c*), above, was reiterated by a number of the club's former members in terms of the hospital's policy of segregation of the sexes, and their close supervision when together at work or socially. Generally, the patients wanted some kind of safeguard, so that if they were to attempt a reorganization of the club, nothing like that which occurred before would happen again. One patient (I.) said that before he rejoined, a charter would be necessary from the state capital. Others wanted assurances from us that their personal belongings would not be destroyed again, and some asked only that someone from the administration be available to guarantee the club's continued existence and implement the patient's suggestions. "There should be rules and regulations." "The club needs a sponsor." "There are lots of good ideas but no one to push them." There were mixed feelings expressed by many of the club's elder male members about the reintroduction of women into the club. It was apparent that it was felt to be a danger in the future because of the fear that the club

had been closed because of a mixing of the sexes. "Some patients have to be kept in line." "Mixing [of the sexes] is all right for outside but not here." One patient (G.) said: "I won't join the club again. A patient doesn't know whether he's coming or going around here."

In March, 1956, the club meetings began again with a nucleus of previous members. Prior to the first meeting certain members who had been active in the attempt at reorganization showed improvement in their ability to relate directly and clearly about club matters, whereas they had previously spoken in a delusional and incomprehensible manner or were mute.

At the first meeting three of the patients had a change of clothes which they effected before the meeting started. As before, the club structure was democratic. Dues of 10¢ monthly were levied, although a plea was made by some members that this would have to be voluntary as it otherwise might exclude from membership some excellent potential members. There was a suggestion that the meeting be used for social purposes, but this was strongly vetoed. When describing the purposes of meeting, one of the patients said we "meet to meet." One patient sat facing away from the other club members and yet was included in a bantering way; and as the meeting progressed, he turned toward the other participants and edged his chair closer. Inappropriate behavior was handled by direction ("just raise your hand and say 'yes' when asked a question") and by condemnation ("That isn't right," or "You can't do that") by the more reality-oriented members. There were bizarre, delusional, and sometimes incomprehensible personal verbalizations, but each member was allowed to say what he wished for the most part, and was listened to attentively.

It was striking that some patients were mute, but they were included in the meeting by words and gestures from the other members and responded with movements of the body and facial expressions. Sometimes a previously mute patient was able to speak along lines already laid down by the verbal members, but only in areas concerning the club. Lastly, some members, once having an indication about what to discuss concerning the club, were able to move on to areas such as their families and former friends. Of note, a divergent strabismus of some of the patients alternated and changed when these members were involved in the transactions of the club with other patients or with us.

The club has continued to meet, with perhaps less success than in the past. After two meetings, we received a letter from one of the club members, a man usually megalomanic and delusional. The following are excerpts:

"Kindly advise us when you are able to come to The Old Timers' Club. Try when you do come to see that the wards by you can be approved sending a group to make it [the meeting] more interesting. According— . . . . "P. S. Understanding doctors should be in front of such patients and make themselves known in the institution for the better of patients and everybody else."

Comment

The mental hospital is a social community with its attitudes, stereotypes, and pressures mirroring and mimicking the community beyond the hospital fence. One could hardly argue today that the patient in a state hospital enters a "social vacuum," as Myerson [19] claimed in 1939; and there have been many recent papers and books emphasizing the transactions that take place in the milieu of the mental hospital.[2,7,22,26] It has been noted that attitudes of interest, kindliness, and tolerance; the relationship of patients to ward personnel; proper treatment facilities, and even hospital architecture have meaning. Caudill and associates,[5] in a private hospital setting, noted the effects on patients of pressures for attitudes toward (*a*) therapist and therapy, (*b*) nurses and other hospital personnel, (*c*)

other patients, and (*d*) themselves. They showed that the patients' attitudes about themselves and about treatment influenced and facilitated therapy even in this private hospital, where psychotherapy ranked highest in a value system of therapies. Menninger,[18] in 1942, divided the necessary functions of the mental hospital into four aspects: (1) personnel, (2) physical plant, (3) organization, and (4) treatment plan. In the state hospitals, there are very few personnel, physical plants are overcrowded, organization and treatment plans are at a minimum, and what few doctors are available have little time to engage in daily face-to-face psychotherapy. The nurses have supervisory duties almost exclusively, and it is the attendants who deal directly with the patients. It is common to find "ward workers," designated from among the patients by the attendants, who control and direct the majority of the patients on many wards, and often such ward workers are the major social stimulus and source of interaction for the patient. If the psychotic patient makes any effort toward interpersonal communication, it must inevitably be toward the untrained personnel of the lowest administrative echelon or toward other patients. Bateman and Dunham[2] have shown that relationships with the "attendant culture" can be antitherapeutic in impeding recovery and facilitating regression. Others[6,25] have reported that recovery often begins when the patient can identify with the attendant and other hospital personnel. The existence of this club in a state hospital indicates that, just as there are pressures for attitudes toward other patients and themselves in the heterogeneous population of the private hospitals, so, too, the patients in the more homogeneous (schizophrenic) chronic state hospital population develop attitudes toward and relationships among themselves. The meaning of these relationships when they occur in groups, and the possible therapeutic use to which they can be put, is the subject of this discussion. We also raise the question of the existence of such autonomous groups in the presence of a stimulating milieu. We feel that the functions of The Old Timers' Club, as outlined above, have demonstrated that there is some intrinsic element in autonomous groups that is therapeutically helpful and which may be lost in developing an active milieu under staff supervision.

Evidence that the needs fulfilled by The Old Timers' Club had their therapeutic aspect lies in the fact that there was great push to have it reorganized, although the majority of its members were disturbed, suspicious, and paranoid patients. The patients in leadership capacity in the club operated on a more appropriate social level, particularly in the context of the club. Some of its officers were discharged within short times after assuming their positions of responsibility (with the exception of the patient who was president at the time of the club's artificial end). The club seemed to give its members the self-esteem coincident with a sense of belonging—a feeling of something special in a hospital community, where there is little to distinguish one patient from another. It allowed patients to participate more fully in hospital life. It gave each of its members the opportunity to test his ability to socialize in a more appropriate milieu than the hospital ward. It allowed individual members with little ego organization to operate in a more appropriate and organized way in the setting of the club. Further, the choice of a democratic structure in spite of the administration's more autocratic structure may not be accidental. Lippitt and associates,[15,17] in a series of experimental studies with boys' groups, showed that the democratic atmosphere was more conducive to constructive work, was less hostile, and generated less tension than autocratic groups. Lindemann,[16] in a preliminary study of the group, felt that group activity allows for conflict-free expression of hostility with the utilization of substitute objects. However, not enough information about the possible existence of such clubs in other institutions

is available to permit one to generalize from this one instance.

The formation of group relationships and their persistence was noted by Jenkins and Curran [13] in 1940 on an admitting and observation ward of a mental hospital. Others [10,14,20] have shown that group work on wards with psychotic patients has led to more participation, more social interaction, more positive ward living, and an increased movement toward individual improvement and discharge. Of historical note and interest is Charles Dickens' sketch,[8] in 1842, of a visit to an asylum in which the salutory effects of a sewing club in controlling aggressiveness of patients was seen. Almost a century later, in 1940, Blackman [4] showed the positive effects of a literary club in the group therapy of schizophrenics. In 1941 Bierer and Haldane [3] reported on a self-governed patient social club which aided in rehabilitation and discharge of patients. Further, discharged patients could continue to attend club functions. Later, at Boston Psychopathic Hospital, Hyde and Solomon [12] reported on patient government as a new form of group therapy which primarily afforded large groups of patients a therapeutic hospital experience.

On the other hand, it has been argued that the club is an expression of rebellion against the hospital, as the *sub rosa* prisoner groups [11] are against the prison administration. As in prisons and many other enforced institutional settings, the function of such groups is to handle boredom and apathy,[9] but, in addition, the rebellion here is constructive and attempts to structure a setting in which the patient-member can operate more appropriately. In this case the club actually detoured about the attendant culture, which, in its efforts to maintain the *status quo*, seemed to impede the patients' move toward health.

Some investigators [6] and members of the administration at the Chicago State Hospital have raised the question of whether such a club facilitates regression. There is much evidence in this instance of increased activity and acceptable social behavior in the members, an increased use of appropriate social conventions, attempts to deny the more regressive aspects of state hospital life, and movement of some of the previously more regressed members of the club toward the behavior of the less regressed members. One might also ask: Does not the club lengthen the stay of the patient in the hospital by providing him with a comfortable club house in which to settle down, when this is not possible on the wards? Although the club allowed some of the patients to make a more effective transference to the hospital,[21] there is evidence that some members of the club, particularly those in positions of responsibility, improved enough so that discharge from the hospital was possible, when such improvement was less evident prior to the club's existence. Many other members improved enough to be more socially effective, although remaining in the hospital. There might be some concern that the more active, manipulative patient would lead the club membership into nonconstructive, and even dangerous, situations. Although some patients in leadership positions were obviously disturbed and active, there is every indication that the learning was constructive, the activity useful, and the group able to exert a controlling and moderating influence on even the most disturbed member.

The attitudes of the personnel toward the club merit some further discussion. During most of the period of the club's existence the attitude of the administration was that of benevolently ignoring its existence, and occasionally being of assistance by indirectly providing material for the club. How can we explain the sudden change in attitude which resulted in the breaking up of the club and the burning of all its property without thought of its significance to the group? It is felt that this action was a manifestation of angry feelings of certain of the hospital staff toward the highest levels of the hospital administration, who were initiating many new changes in line

with their thinking about active milieu therapy. The medical director was desirous of seeing the patients develop more socially mature kinds of relationships and was actively trying to develop this throughout the hospital. Any increase of patient autonomy was seen as threatening to personnel, who were already feeling a loss of prestige because of the medical director's actions, which were stripping them of some of their power in the total situation and turning over responsibility for behavior to the patients themselves. Attendant personnel seem to do best when patients are apathetic, amusing, or helpful to the attendant group, e. g., in running errands. The active, acutely disturbed patients are handled with wariness, distance, and an attempt to make them conform to the ward policies of "no acting up," or "out." To admit that the patient can act in any area in a more mature manner would necessitate the attendants and other personnel giving up the "adult-child role" with the patients and the adoption of a new role, not yet spelled out, and therefore anxiety-provoking.

Disbanding the club, then, had this double-barreled effect: First, it diminished some of the patient autonomy known to exist *sub rosa;* and, second, it was a way of striking back at the administration, known to favor patient group activity. It is known that both the fire department employee, who issued the fire warning, and the administrative assistant, who so dictatorially carried out the order to clean up the club house, were under stress at the time—the former with his personal life, the latter with respect to his administrative position. Thus we see that the existence of autonomous clubs depends not only on the wishes and needs of patients but also on the attitudes, and often overdetermined feelings, of hospital personnel.

This discussion has raised more questions than it has answered, and properly so. For there is a need for further investigation of such clubs as this. Too little is known about them to determine why such groups continue to operate, while others, formed by the hospital with as many or more facilities, have failed. Do they offer the patient something which cannot be duplicated by more directive efforts? Perhaps there is something in the very nature of the schizophrenic illness for which less, rather than more, control and direction is desirable. What is the effect of such club activities upon the social adjustment of the patient who leaves the hospital? Investigators have indicated that it can facilitate the remission of symptoms. Lastly, should such autonomous clubs be looked for and encouraged in hospitals undertaking more active milieu programs? Other, less formally structured patient clubs, known to us, have arisen from time to time in a private mental hospital with an active milieu program. From discharged patients' retrospection, their club's major function was to increase the self-esteem of the member-patients, who for the most part had a neurotic, rather than a psychotic, symptomatology.

These are all questions for which we have offered only tentative answers because of the paucity of information about such groups. It is hoped that this presentation will encourage others to look for autonomous groups and report upon them, so that a body of information will develop from which one may discern their meanings and more effective ways of utilizing them.

Psychosomatic and Psychiatric Research Institute, Michael Reese Hospital (16).

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Books

BOOK REVIEWS

Le délirium tremens. By R. Coirault and H. Laborit. Price, 1,200 fr., Pp. 140, with 21 figures. Masson & Cie, 120 boulevard Saint-Germain, Paris, 6°, 1956.

This study is the result of an attempt to find a more rational and effective treatment of a syndrome caused by the ingestion of ethyl alcohol which is increasing alarmingly in France.

One of the difficulties in the study is the lack of any sharp definition of the syndrome called delirium tremens. This is the principal cause of the extremely varied statistics dealing with the problem and the principal difficulty with establishing the value of any treatment. The syndrome goes over, on the one hand, into the simple transitory periods of confused delirium common in acute alcoholism and, on the other hand, into the serious acute delirium of the hyperazotemic. Recognizing the impossibility of giving pathognomonic signs for the disorder, the authors insist on the following differential points of the clinical picture.

The elevation of the temperature is more important than in the acute confusional attack but less elevated than in the acute azotemic delirium; the confusion in delirium tremens lacks the appearance of perplexity characteristic of the other syndromes; there are abnormal movements of chewing, sucking, and grasping which are missing in the others; the psychomotor agitation lasts much longer—the delirium tremens patient scarcely sleeps at all.

As a result of a detailed biochemical and bioelectrical study of such patients, the authors conclude that the essential phenomenon is a triad of *hyperkalicytie, hypokaliémie, hypokaliurie.* This concentration of the calcium ions in the cells of the body results in a low calcium in the blood and a low excretion in the urine. It results also in a general neuromuscular hyperexcitability, but with a disequilibrium between the excitability of nerve and muscle, as measured by the chronaxie.

In their discussion, the authors admit the fundamental importance of psychological factors for the initiation of the excessive drinking but dismiss them as irrelevant to their immediate problem of finding a treatment for the acute delirium, which appears to them as an acute paroxysm of acidosis during a chronic alcoholism, producing a state of insomnia provoked by hyperexcitable afferent circuits passing via the activating reticular formation, maintaining the hypertonus of the diencephalic vigilant centers. On these grounds they instituted an antiacidotic method of treatment (vitamin B) which would tend to restore the balance of Ca ion in the blood and tissues (cortisone, steroids), correct the decarboxylation (vitamin B, magnesium), and lower the hyperexcitability of the activating reticular system either directly (chlorpromazine, magnesium) or indirectly at the periphery (anesthetic steroid).

A series of case histories is given illustrating the details of the method of treatment, an essential factor of which is a new anesthetic steroid called *succinate sodique de 21-hydroxy pregnandione.*

The authors state in a footnote that since the report of their study they have treated 20 patients successfully either with chlorpromazine and cortisone, in the major confusooneiroid form, or with the anesthetic steroid, in delirium tremens. The recovery obtained is said to have been extremely rapid. The claim of the authors to have found a rapid and effective treatment of this distressing syndrome should be controlled in other clinics.

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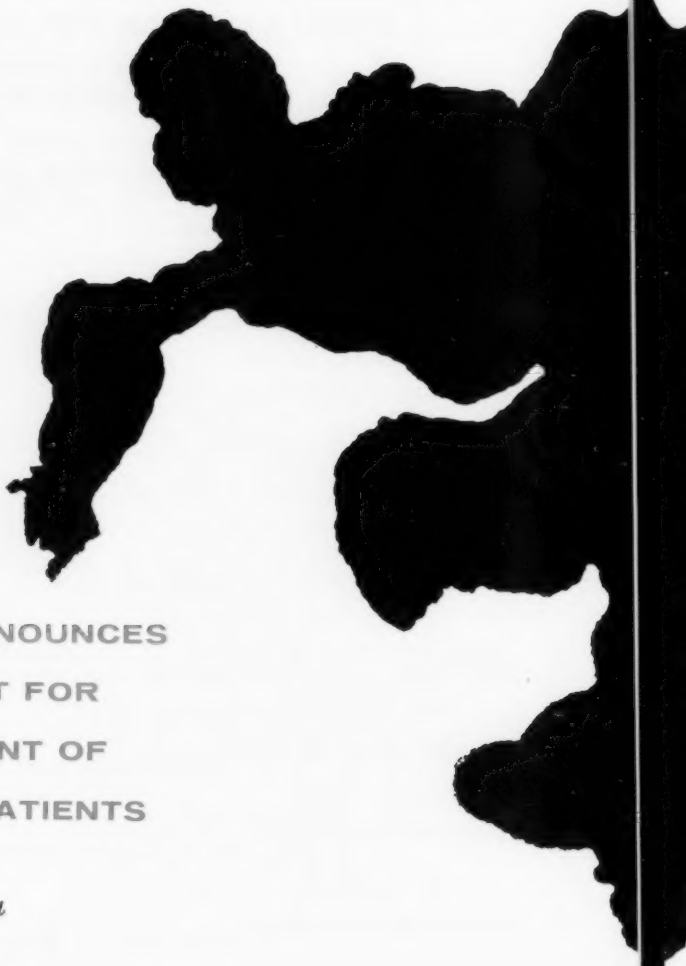

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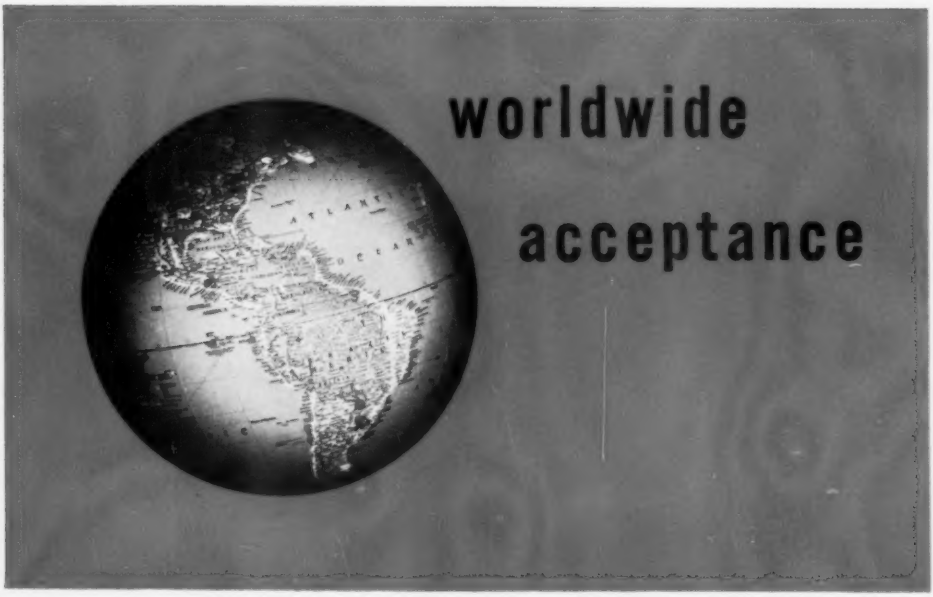

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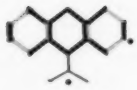

1. 10- to 12-hour therapeutic effect with a single dose in the morning allows ambulatory patients to carry out their daily routines without interruption for medication.
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3. Breakthrough of symptoms is eliminated because the sustained release of medication prevents drops in therapeutic level. A dose at bedtime promotes good sleeping habits, too.

Smith Kline & French Laboratories, Philadelphia

Available in four strengths: 30 mg., 75 mg., 150 mg. and 200 mg.

'THORAZINE'
chlorpromazine, S.K.F.

SPANSULE
sustained release capsules, S.K.F.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F. †T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.